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99 BB CNRURE

NOVEL STABILIZED ACTIVATED DERIVATIVES OF
CARBAMIC ACID, THEIR PROCESS OF PREPARATION AND THEIR
USE FOR THE PREPARATION OF UREAS

5 This is a continuation of co-pending international application PCT/FR00/00080, filed on 14 January 2000, which designates the United States of America.

10 The invention has for its object new stable activated derivatives of carbamic acid, particularly new stable activated carbamates, their process of preparation and their use for the preparation of urea.

The synthesis and applications of substituted ureas has for several years undergone great development. These compounds are present in a certain number of active principles now under development in the pharmaceutical industry as protease inhibitors of VIH, antagonists of the CCK-B receptor, or antagonists of endothelin ¹. Moreover, the oligoureas have been introduced as "scaffolds" for the creation of β -sheets ² or as mimics of the peptide skeleton ³. The methods of formation of substituted ureas rely on the reaction of amines with carbonylation agents ⁴, with isocyanates ⁵ or with carbamates ⁶.

25 In the field of research looking toward the development of new compounds with immunomodulatory activity, there is needed a simple method, not requiring the use of phosgene or of one of its derivatives, to produce easily peptidic analogs containing ureas or urea oligomers. In 1995, the Burgess group described for the first time the synthesis in 30 solid phase of oligoureas. This was based on the use of isocyanate synthons derived from N-protected mono-phthalimide diamines. This strategy requires the preparation of protected mono-phthalimide diamines precursors and uses triphosgene as the carbonylation agent

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to obtain the corresponding isocyanate ^{3a, 3b}. In a similar approach, the Schultz group used azido 4-nitrophenyl carbamates as pre-activated synthons ^{3c, 3d}. More recently, 4-nitrophenyl carbamates obtained by the reaction of Boc-protected N-substituted ethylenediamines with 4-nitrophenyl chloroformate have been described as synthons for the synthesis of urea-peptoids by the Liskamp group ^{3e}. In short, there does not exist at present an easy synthesis route for activated monomers obtained from amino acids protected or not by an Fmoc, Boc or Z group, avoiding the use of phosgene (or its derivatives) and permitting the synthesis of urea oligomers as well as the easy incorporation of urea patterns in peptides. The activated carbamates are generally prepared by the reaction of amines with carbonates ^{4c} or chloroformates ^{3e, 6b}, or by reaction of isocyanates with alcohols ^{6a}.

One of the aspects of the invention is to provide novel stable activated derivatives of carbamic acid, in particular novel stable activated carbamates.

One of the other aspects of the invention is to provide novel isocyanates.

One of the other aspects of the invention is to provide a novel process for the preparation of urea, cyclic or not.

One of the other aspects of the invention is to provide
25 novel ureas, cyclic or not.

Generally speaking, the invention has for its object the use of isocyanates obtained from amino acid derivatives for the preparation and if desired the isolation of stable activated derivatives of carbamic acid or of stable

According to a preferred embodiment, the invention relates to the use of isocyanates, of stable activated derivatives of carbamic acid, or of stable activated carbamates defined above, for the preparation of

substituted ureas, cyclic or not, particularly of oligomers of ureas, cyclic or not, or for the preparation of peptides or pseudo-peptides containing urea designs, cyclic or not.

By "amino acid derivatives", is meant amino acids (alpha, beta, gamma, delta-aminated, or the like) whose primary or secondary amine function can be protected by a group selected to give a tertiary amine function, urethane, amide, urea, nitro or phthalimide.

Within the meaning of the invention, the term "amino acid derivatives" should be interpreted in its broad sense, as understood by those in the art, and designates particularly a derivative of peptide, polypeptide, protein, pseudopeptide or oligoureia.

By "activated carbamate" or "activated derivative of carbamic acid", is meant a carbamate or a carbamic acid derivative capable of reacting with primary or secondary amines or with alcohols in the presence of not of a base in an organic solvent and generally at ambient temperature.

By "stable carbamate" or "stable carbamic acid derivative", is meant a stable carbamate or a stable derivative of carbamic acid because it is isolable, purifiable and can be stored (preferably at 4°C) for a period of at least 3 months without noticeable degradation. The stability can be measured for example by the following test: HPLC or thin layer chromatography.

By "isolation" is meant the process of separation of the desired product from all of the impurities present in the reaction mixture (the latter can be for example: an excess of one of the reagents used to carry out the reaction, symmetrical urea, the amine obtained by the rearrangement of isocyanate in the presence of water) and the recovery of the thus-purified product in a form permitting it to be stored (preferably at 4°C) for a long

period (several months, at least 3 months) without noticeable decomposition.

The expression "urea oligomers" means a successive chain of motifs interconnected by urea linkages (at least two)

For example: $\text{NH}_2-\text{CHR}_1-\text{CHR}'_1-\text{NH}-\text{CO}-\text{NH}-\text{CHR}_2-\text{CHR}'_2-\text{NH}-\text{CO}-\text{NH}-\text{CHR}_3-\text{CHR}'_3-\text{CONH}_2$

The invention particularly has for its object a process for the production of stable activated derivatives of carbamic acid, from an amino acid derivative in which the amino group is protected, comprising:

- a) a step of transforming the -COOH group of the amino acid derivative into the -CON₃ group to obtain an acyl azide,
- b) a step of transforming the -CON₃ group of the acyl azide into the -NCO group to obtain an isocyanate,
- c) a step of treating the isocyanate to obtain said stable derivative of carbamic acid.

According to a preferred embodiment of the process of the invention, step a) for the transformation of the -COOH group into the -CON₃ group, is carried out by a treatment, with the nitride anion, of an activated derivative of the amino acid in which the amino group is protected.

By way of example, the nitride anion could be used in the form of sodium azide.

Thus, step a) of transformation of the -COOH group into the -CON₃ group could be carried by treatment of the mixed anhydride (formed from the amino acid derivative) with sodium azide.

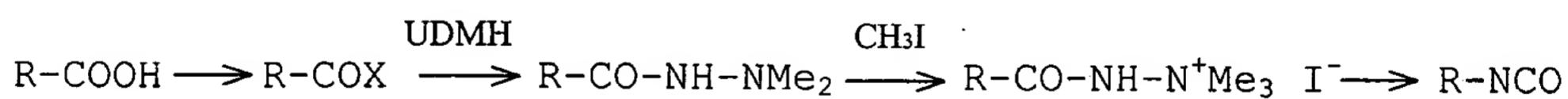
Generally speaking, any method known to those skilled in the art permitting obtaining an azide from an acid can be used, and particularly those described in the encyclopedia of Houben-Weyl, "Methoden der organischen Chemie".

According to another preferred embodiment of the process of the invention, step a) for transformation of the -COOH group into the -CON₃ group is carried out by the treatment, with hydrazine, of an activated amino acid derivative in which the amino group is protected, to obtain a hydrazide, which is then subjected to conversion to a nitrite.

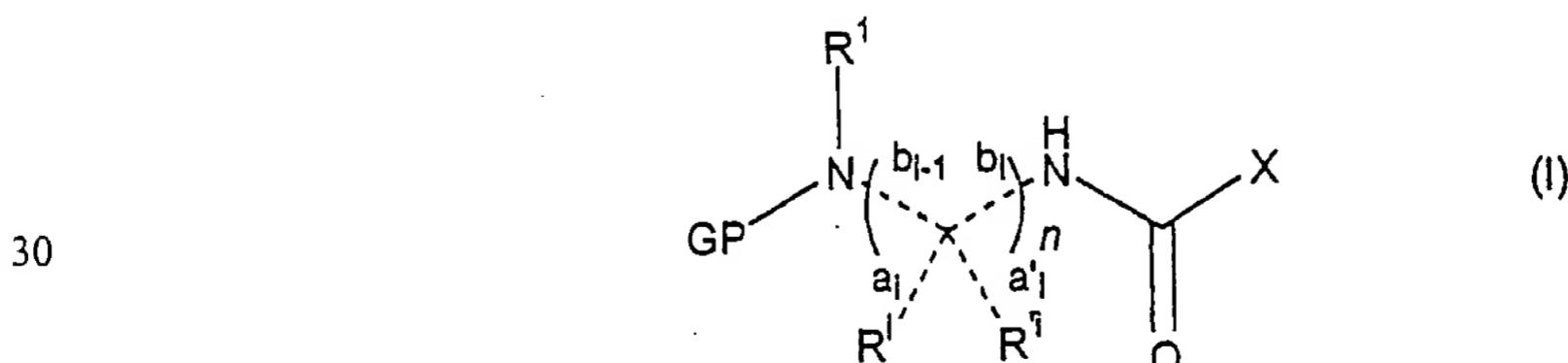
By "activated derivative of amino acid" is meant for example an acid ester or an acid halide, such as an acid chloride.

By way of example, carboxylic acid is first converted to an active derivative (ester, chloride etc...) that the action of hydrazine transforms into a hydrazide, which is then transformed into the desired acyl azide, by the action of nitrous acid.

According to another preferred embodiment of the invention, the transformation of the -COOH group into the -NCO group can be carried out by the method using unsymmetrical disubstituted dimethylhydrazine ("UDMH"), according to the synthesis reaction indicated below by way of example:



The invention also has for its object compounds according to the formula (I):

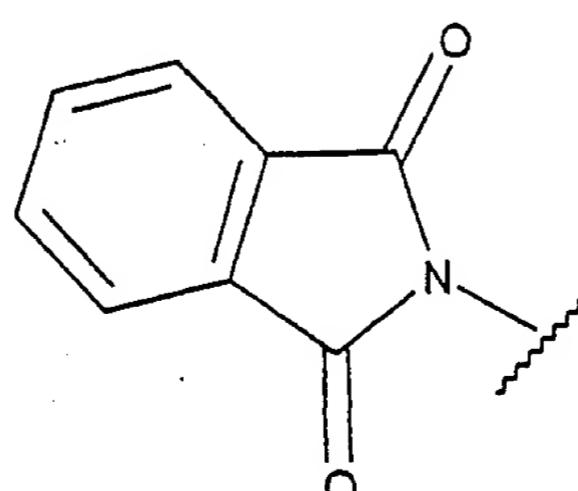


in which

- "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- "i" is a whole number varying from 2 to $n+1$,
- " a_i and a'_i ", shown by a dotted line, are covalent bonds which can be single (s) or double (d),
- 5 " b_i and b_{i-1} ", represented by broken lines, are covalent bonds which can be single (s), double (d) or triple (t), provided that:
 - * b_1 and b_{n+1} are always single bonds (s),
 - * if $b_i = d$, then a_i and $a_{i+1} = \emptyset$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$
 - 10 * if $b_i = t$, then a_i and $a_{i+1} = \emptyset$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$
 - * if $a_i = d$, then b_{i-1} and $b_i = s$,
- 15 certain of these linkages a_i , a'_i , b_{i-1} can also form parts of aromatic rings,
- GP is a protective group selected from:
 - * oxycarbonyl (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),
 - * acyl (GP = RCO), preferably R = CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
 - * alkyl (GP = R), preferably R = trityl, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
 - * aryl, particularly phenyl,
 - 25 * urea (GP = RNHCO), preferably R = H, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,
 - * phthalimide ($R^1 = \emptyset$)

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* O₂ (corresponds to a nitro group masked with amine),
R¹ = Ø

- the groups R¹, Rⁱ, R'ⁱ and R can each represent
5 independently one of the other:

hydrogen,

halogen,

the side chain of amino acid selected from natural or
synthetic amino acids,

10 an alkyl (C1-C20) group, substituted or not with one or
several of the following substituents:

1/ -COOR_a

2/ -CONHR_a

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR

7/ -NH₂

8/ -NH(CO)R_a

9/ aryl, whose cyclic structure contains 5 to 20
carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

25 13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20
carbon atoms

an alkoxy group OR_a

30 an NH₂ group

an OH group

-COOR_a

-CONHR_a

-CONH₂

-CH₂COOR_a

-CH₂CONHR_a

-CH₂CONH₂

R_a representing an alkyl group of 1 to 20 carbon atoms,
5 or an aryl group whose cyclic structure contains 5 to 20
carbon atoms,

10 - the group X represents a group conferring on the compound of formula I an activated carbamate structure, which X group comes from a compound selected particularly from phenol, if desired substituted with at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

- 15 - N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 20 - 4-aza-1-hydroxybenzotriazole (4-HOAt)
- tetrazole
- imidazole

30 the compound of formula (I) having the following property:

- if one or several asymmetric carbons are present in the formula (I), then their configuration can be independently either D (dextro) or L (levo),

- the groups R^1 , R^i , R'^i can also be defined on the basis of intramolecular cyclizations which are as follows:

— 1/ cyclization between R^i and R'^i

5 2/ cyclization between R^i or R'^i and R^{i+kc} (where kc is a positive whole number, preferably from 1 to 3)

3/ cyclization between R^1 and R^i or R'^i wherein preferably $i=2, 3$ or 4 ,

provided that the compound of formula (I) is different from the following compounds, in which:

10 - $n=2$, $GP=Boc$, $R^1 =$ isobutyl, $R^2=R'^2=R^3=R'^3=H$, $X = 4-$ nitrophenol,

- $n=2$, $GP=Boc$, $R^1 =$ benzyl, $R^2=R'^2=R^3=R'^3=H$, $X = 4-$ nitrophenol,

- $n=2$, $GP=Boc$, $R^1 = CH_2-p-C_6H_4Ot-Bu$, $R^2=R'^2=R^3=R'^3=H$, $X = 4-$ nitrophenol,

- $n=2$, $GP=Boc$, $R^1 = H$, $R^2=R'^2=R^3=R'^3=H$, $X = 4-$ nitrophenol.

The first bond b_1 and the last b_{n+1} each connected to a nitrogen atom, are always single bonds: $*b_1$ and b_{n+1} are always single bonds (s).

If a b_i bond is double, this implies that the adjacent bonds b_{i-1} , b_{i+1} , a_i and a_{i+1} are single bonds and that the bonds a'_i and a'_{i+1} do not exist:

* if $b_i = d$, then a_i and $a_{i+1} = s$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$

If a b_i bond is triple, this implies that the adjacent bonds b_{i-1} , b_{i+1} are single bonds and that the bonds a_i , a'_i , a_{i+1} and a'_{i+1} do not exist:

* if $b_i = t$, then a_i and $a_{i+1} = \emptyset$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$

If an a_i bond is double, this means that the adjacent bonds b_{i-1} and b_i are single bonds and that the bond a'_i does not exist.

* if $a_i = d$, then b_{i-1} and $b_i = s$.

The symbol \emptyset corresponds to the absence of the bond to which it relates.

5 The expression "certain of the bonds could also be part of aromatic rings, substituted or not" can be explained in the following manner. These cases can occur:

$n \geq 2$: the bonds a_i , a_{i+1} , and b_i belong to the aromatic cycle; the bond b_{i+1} is in the ortho position relative to the b_{i-1} bond.

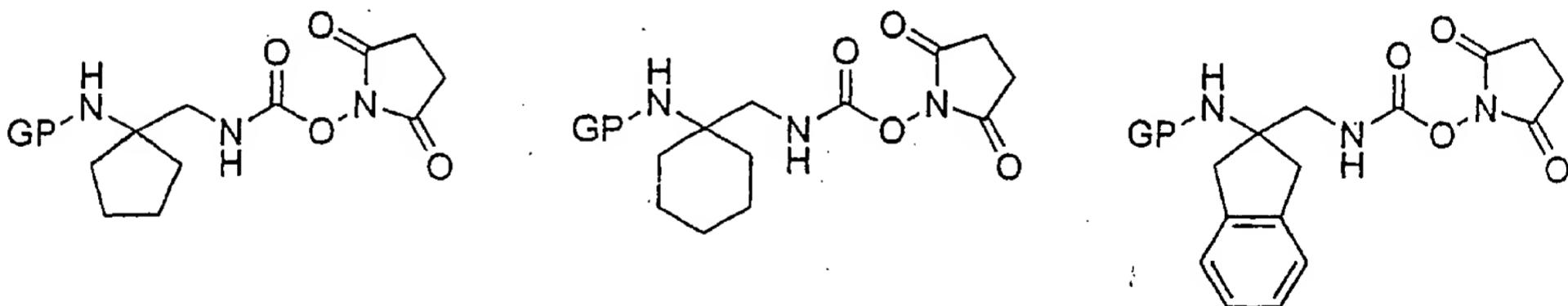
10 $n \geq 3$: the bonds a_i , a_{i+2} , b_i and b_{i+1} belong to the aromatic cycle; the b_{i+2} bond is in the meta position relative to the b_{i-1} bond.

15 $n \geq 4$: the bonds a_i , a_{i+3} , b_i , b_{i+1} and b_{i+2} belong to the aromatic cycle; the bond b_{i+3} is in the ortho position relative to the b_{i-1} bond.

If there is cyclization between R^1 , R^i and R'^i , they can be illustrated in the following manner:

1/ Cyclization between R^i and R'^i :

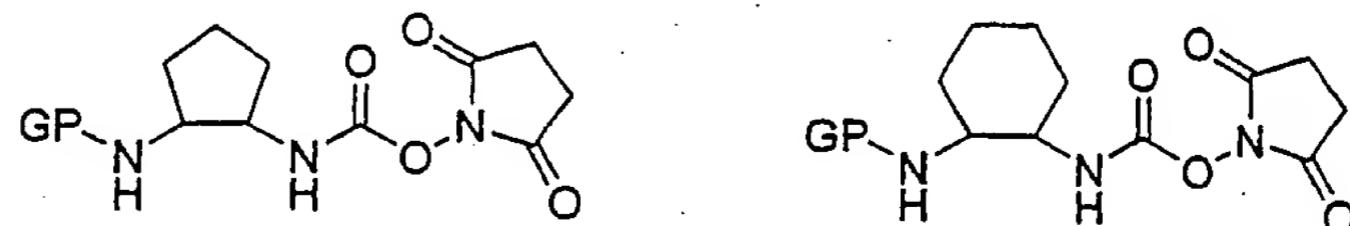
by way of illustration, the three following molecules, in which $n=2$, contain cyclization between R^2 and R'^2



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2/ Cyclization between R^i (or R'^i) and R^{i+k} (where k can be a whole positive number comprised between 1 and 3):

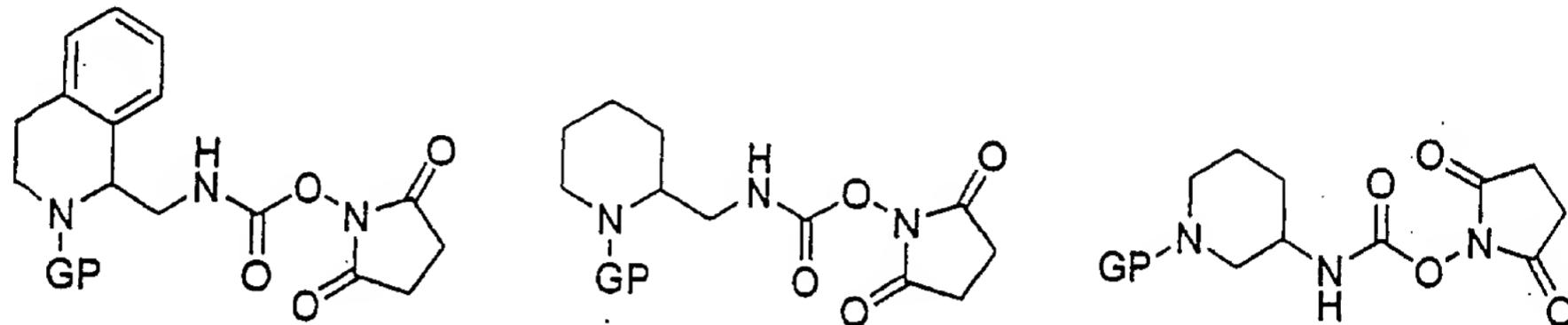
by way of illustration, the three following molecules in which $n=2$, contain cyclization between R^2 and R^3 (in this case k is equal to 1)



3/ Cyclization between R¹ and Rⁱ (or R'ⁱ) wherein preferably i=2, 3 or 4:

5 by way of illustration, the three following molecules in which n=2, contain a cyclization between R¹ and R² (or R¹ and R³)

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In all the formulas indicated above and hereafter, when GP = RCO or ROCO, R preferably represents a hydrocarbon chain.

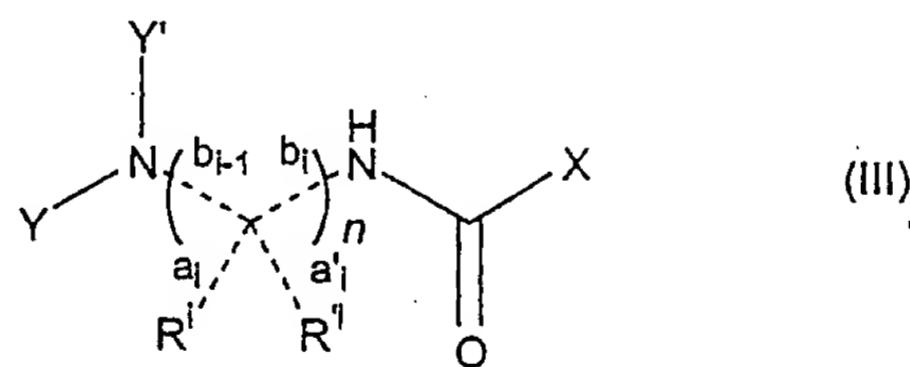
In all the formulas indicated above and hereinbelow, when GP = ROCO, GP forms with the nitrogen atom to which it is contiguous a urethane group.

In all the formulas indicated hereafter, when A = ROCO, A forms with the nitrogen atom to which it is contiguous a urethane group.

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The invention also relates to compounds of the formula (III)

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in which

- "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,
- 30 - "i" is a whole number varying from 2 to n+1,
- a_i and a'_i, represented in broken lines, are covalent bonds which can be single (s) or double (d),

b_i and b_{i-1} , represented by broken lines, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

- * b_1 and b_{n+1} are always single bonds (s),
- 5 * if $b_i = d$, then a_i and $a_{i+1} = s$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$

* if $b_i = t$, then a_i and $a_{i+1} = \emptyset$; a'_i and $a'_{i+1} = \emptyset$; b_{i-1} and $b_{i+1} = s$,

- * if $a_i = d$, then b_{i-1} and $b_i = s$,

10 certain of these bonds a_i , a'_i , b_{i-1} can also form part of aromatic rings,

- the groups R^1 , R^i and R'^i can each represent independently one of the other:

hydrogen,

the side chain of an amino acid selected from natural or synthetic amino acids

a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

- 1/ $-COOR_a$
- 2/ $-CONHR_a$
- 3/ $-COOH$
- 4/ $-OH$
- 5/ $-OR_a$
- 25 6/ $-NHR_a$
- 7/ $-NH_2$
- 8/ $-NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

- 30 10/ halogen
- 11/ carbonyl
- 12/ nitrile
- 13/ guanidine
- 14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

an NH₂ group

5 an OH group

-COOR_a

-CONHR_a

-CONH₂

-CH₂COOR_a

10 -CH₂CONHR_a

-CH₂CONH₂

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- the groups Y and Y' can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide bonds)

A-N(Z₁)-C(Z'₁)(Z''₁)-Ψ₁[*]-...-Ψ_{k-1}[*]-C(Z'_k)(Z''_k)-Ψ_k[*]-...Ψ_{p-1}[*]C(Z'_p)(Z''_p)-Ψ_p[*]-

- p is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

- k is a whole number varying from 1 to p,

- A is a group selected from:

25 * hydrogen

* oxycarbonyl (ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),

* acyl (RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂,

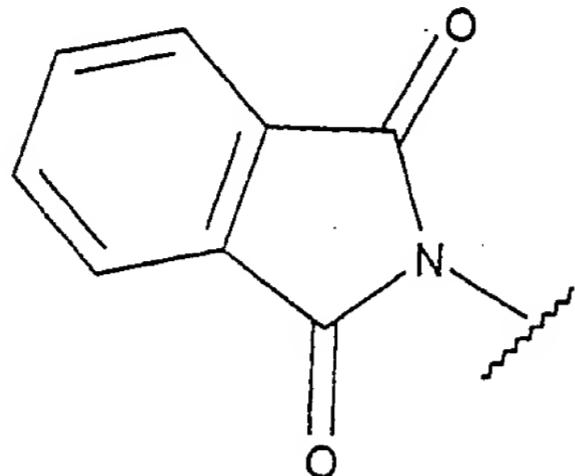
30 C(CH₃)₃, phenyl, benzyl, allyl, aryl,

* alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,

* phenyl, particularly aryl,

- * urea (RNHCO), preferably $\text{R} = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2,$
 $\text{C}(\text{CH}_3)_3$, phenyl, benzyl, allyl,
- * phthalimide ($\text{R}_1=\emptyset$)

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* biotin

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- Z_k, Z'_k and Z''_k can each represent independently one of the other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids

a (C1-C20) alkyl group unsubstituted or substituted by one or several constituents from the following:

- 1/ $-\text{COOR}_b$
- 2/ $-\text{CONHR}_b$
- 3/ $-\text{COOH}$
- 4/ $-\text{OH}, \text{OR}_b$
- 5/ $-\text{NHR}_b$
- 6/ $-\text{NH}_2$
- 7/ $-\text{NH}(\text{CO})\text{R}_b$

25

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

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12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

$-\text{OR}_b$

-COOR_b
-CONHR_b
-CONH₂
-CH₂COOR_b
5 -CH₂CONHR_b
-CH₂CONH₂

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

10 - -ψ_k[*]- are independently either peptidic linkages CO-NH or bonds of different chemical nature selected particularly from the following list, which is not limiting:

15 ψ_k[*]- = -CH₂CH₂ ; -CH(F_k)=CH(F_{k'})- ; -CH₂NH- ; -NHCO- ;
-NHCONH- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ; -CH₂- ;
-CH(F_k)- ; -CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCONF_{k'}- ; CH₂-
CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_{k'})CONH-

20 F_k and F_{k'} representing, independently from each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

2/ an amino acid residue or an amino acid chain:

25 A-N(Z₁)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-
C(Z'_m)(Z''_m)-CO-

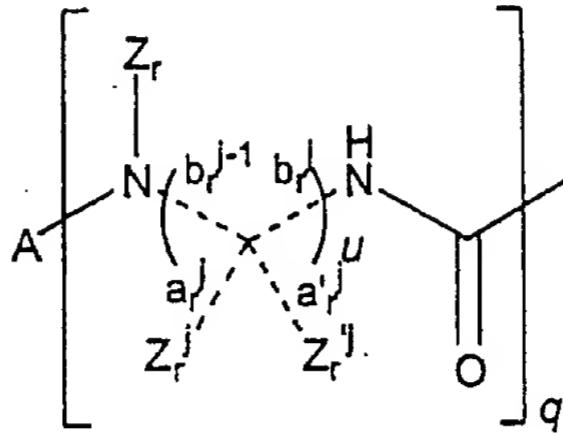
- m is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- k is a whole number varying from 1 to m,

30 - A defined as above

3/ an oligomer of urea having the following formula:

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- "u" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

10 - "q" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

- "j" is a whole parameter greater than or equal to 2 defined in the following manner: j always has whole values comprised from 2 to u+1,

- or "r" is a whole parameter greater than or equal to 1, always taking values comprised from 1 to q,

- "a_r^j" and "a'_{r'}^{j+1}" represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j" and "b_r^{j-1}" represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s)

* if $b_r^j = d$, then a_r^j and $a_r^{j+1} = s$; $a'_{r'}^j$ and $a'_{r'}^{j+1} = \emptyset$;
 b_r^{j-1} and $b_r^{j+1} = s$

25 * if $b_r^j = t$, then a_r^j and $a_r^{j+1} = \emptyset$; $a'_{r'}^j$ and $a'_{r'}^{j+1} = \emptyset$;
 b_r^{j-1} and $b_r^{j+1} = s$

* if $a_r^j = d$, then b_r^{j-1} and $b_r^j = s$

certain of these bonds can also form a part of aromatic rings,

30 - A defined as above

- Z_r , Z_r^j , $Z'_{r'}^{j+1}$ are defined independently as above for R^1 , R^i , R'^i ,

- the X group represents a group giving to the compound of formula I an activated carbamate structure, which X group comes from a compound selected particularly from phenols, if desired substituted by at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)
- imidazole
- tetrazole

the compound of formula (III) having the following property:

- if one or several asymmetric carbons are present in the formula (III), then their configuration can be independently either D (dextro) or L (levo),

- the groups R^1 , R^i , R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

- 1/ cyclization between R^i and R'^i
- 2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a whole positive number, preferably comprised between 1 and 3)

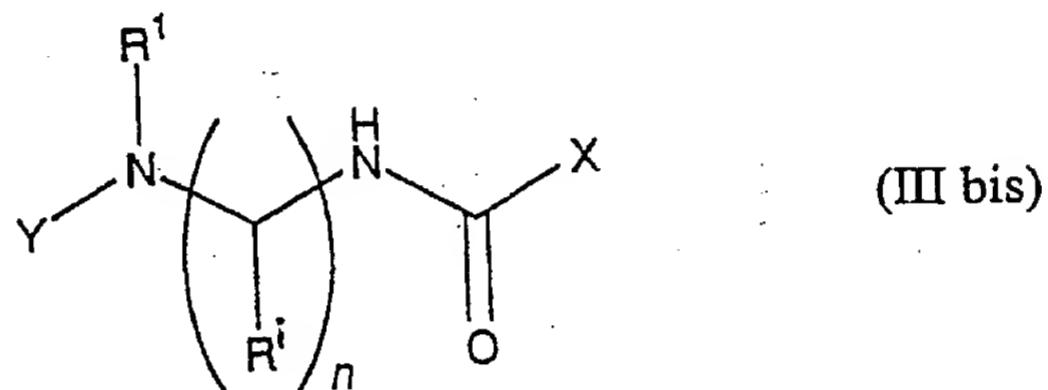
3/ cyclization between R^1 and R^i (or R'^i) wherein preferably $i=2, 3$ or 4 .

As an example of a pseudopeptide entering into the definition of Y, can be cited:

5 Boc-Ala-Ala-Gly-Ile-Gly-[CH₂NH]-Ile-

(pseudo-hexapeptide containing a bond of the reduced type between Gly and Ile)

10 The invention also has for its object compounds of formula (III bis)



in which

- "n" is a whole number greater than or equal to 1, preferably 1 to 10, preferably 1 to 4,

- "i" is a whole number varying from 2 to $n+1$,

- the Y group can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

A-N(Z₁)-C(Z'₁)(Z''₁)-Ψ₁[*]-C(Z'₂)(Z''₂)-Ψ₂[*]-...-Ψ_{k-1}[*]-C(Z'_k)(Z''_k)-Ψ_k[*]-...

25 Ψ_{p-1}[*]C(Z'_p)(Z''_p)-Ψ_p[*]-

- "p" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

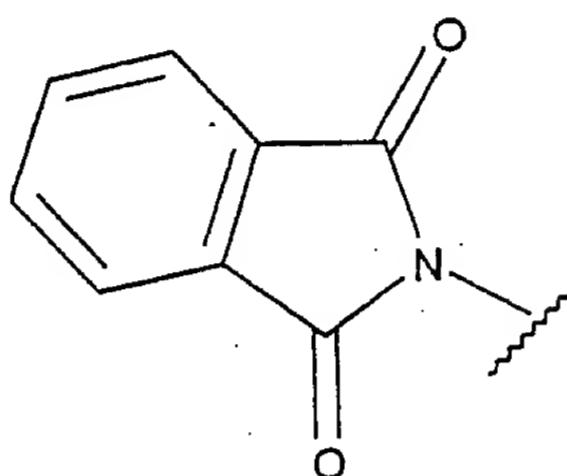
- k is a whole number varying from 1 to p,

- A is a group selected from:

* hydrogen

* oxycarbonyl (ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),

- * acyl (RCO), preferably $\text{R} = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2,$
 $\text{C}(\text{CH}_3)_3$, phenyl, benzyl, allyl, aryl,
- * alkyl (R), preferably $\text{R} = \text{trityl}, \text{CH}_3, \text{CH}_2\text{CH}_3,$
 $\text{CH}(\text{CH}_3)_2, \text{C}(\text{CH}_3)_3$, benzyl, allyl,
- 5 * phenyl, particularly aryl,
- * urea (RNHCO), preferably $\text{R} = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2,$
 $\text{C}(\text{CH}_3)_3$, phenyl, benzyl, allyl,
- * phthalimide ($\text{R}1=\emptyset$)



- 15 * biotin
- * the group A can form with the nitrogen atom N with
 which it is contiguous, an " NH_2^+ " entity
 - Z_k, Z'_k , and Z''_k can each represent independently of
 each other
 - hydrogen,
 - the protected or unprotected side chain of an amino
 acid selected from proteinogenic and non-proteinogenic
 amino acids,
- 20 25 an ($\text{C}1-\text{C}20$) alkyl group, unsubstituted or substituted
 with one or several of the following substituents:
 - 1/ $-\text{COOR}_b$
 - 2/ $-\text{CONHR}_b$
 - 3/ $-\text{COOH}$
 - 30 35 4/ $-\text{OH}, \text{OR}_b$
 - 5/ $-\text{NHR}_b$
 - 6/ $-\text{NH}_2$
 - 7/ $-\text{NH}(\text{CO})\text{R}_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

5 11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

10 -OR_b

-COOR_b

-CONHR_b

-CONH₂

-CH₂COOR_b

-CH₂CONHR_b

-CH₂CONH₂

R_b representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- -ψ_k[*]- are independently either peptid links CO-NH, or linkages of different chemical nature selected particularly from the following list, which is not limiting:

25 ψ_k[*]- = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ;

-CH(F_k)NHCO- ; -N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ;

-CH(F_k)=CH(F_{k'})- ; -CH₂NH- ; -NHCO- ; -NHCONH- ;

-N(F_k)CON(F_{k'})- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ;

-CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_{k'})- ; -CH₂-CONH- ;

30 CH(F_k)CONH- ; -CH(F_k)CH(F_{k'})CONH-

F_k and F_{k'} representing, independently of each other hydrogen, the side chain protected or not of an amino acid selected from proteinogenic amino acids and non-proteinogenic amino acids, halogen, an alkyl group of 1 to

20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

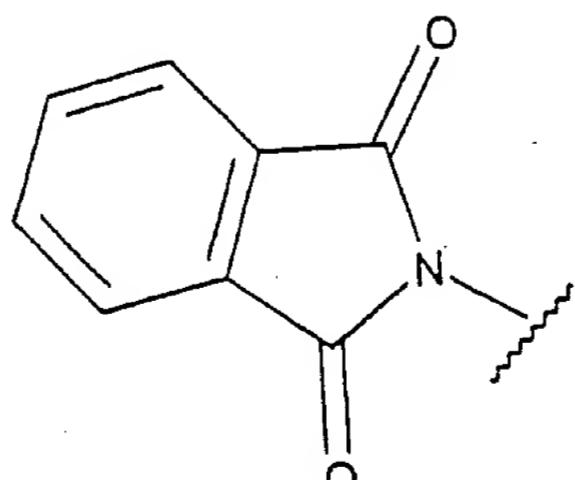
2/ an amino acid residue or an amino acid chain:

5 A-N(Z₁)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-

- "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,
- "k" is a whole number varying from 1 to m,
- A defined as above

3/ a GP group which can be:

- a protective group selected from:
 - * hydrogen
 - * oxycarbonyl (GP=ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),
 - * acyl (GP=RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl, aryl,
 - * alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,
 - * phenyl, particularly aryl,
 - * urea (RNHCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl,
 - * phthalimide (R1=Ø)



30 * biotin

- * O₂ (corresponding to a nitro group as a masked amino form), R₁=Ø,
- the GP group which can also be such that the "GP-N" entity forms an "NH₂⁺" entity,
 - the R¹, Rⁱ and R groups can each represent independently of each other:
 - hydrogen,
 - halogen,
 - the protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids
 - a (C₁-C₂₀) alkyl group unsubstituted or substituted with one or several of the following substituents:
- | | |
|-----|--|
| 1/ | -COOR _a |
| 2/ | -CONHR _a |
| 3/ | -COOH |
| 4/ | -OH |
| 5/ | -OR _a |
| 6/ | -NHR _a |
| 7/ | -NH ₂ |
| 8/ | -NH(CO)R _a |
| 9/ | aryl, whose cyclic structure contains 5 to 20 carbon atoms |
| 10/ | halogen |
| 11/ | carbonyl |
| 12/ | nitrile |
| 13/ | guanidine |
| 14/ | nitro |
| | an aryl group whose cyclic structure contains 5 to 20 carbon atoms |
| 30 | an OR _a group |
| | an NH ₂ group |
| | an OH group |
| | -COOR _a |
| | -CONHR _a |

-CONH₂

-CH₂COOR_a

-CH₂CONHR_a

-CH₂CONH₂

5 R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

10 - the X group represents a group giving to the compound of formula (III bis) the structure of an activated derivative of carbamic acid, which X group comes from a compound selected particularly from phenols, if desired substituted with at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)
- imidazole
- tetrazole

25 30 the compound of formula (III bis) having the following property:

- if one or several asymmetric carbons are present in the formula (III bis), then their configuration can be independently either D (dextor) or L (levo),

5 - the R¹ and Rⁱ groups can also be defined on the basis of intramolecular cyclizations which are as follows:

1/ cyclization between Rⁱ and R^{i+kc} (where kc is a whole positive number, preferably comprised between 1 to 3)

10 2/ cyclization between R¹ and Rⁱ with preferably i = 2, 3 or 4,

provided that the compound of formula (III bis) is different from the following compounds in which:

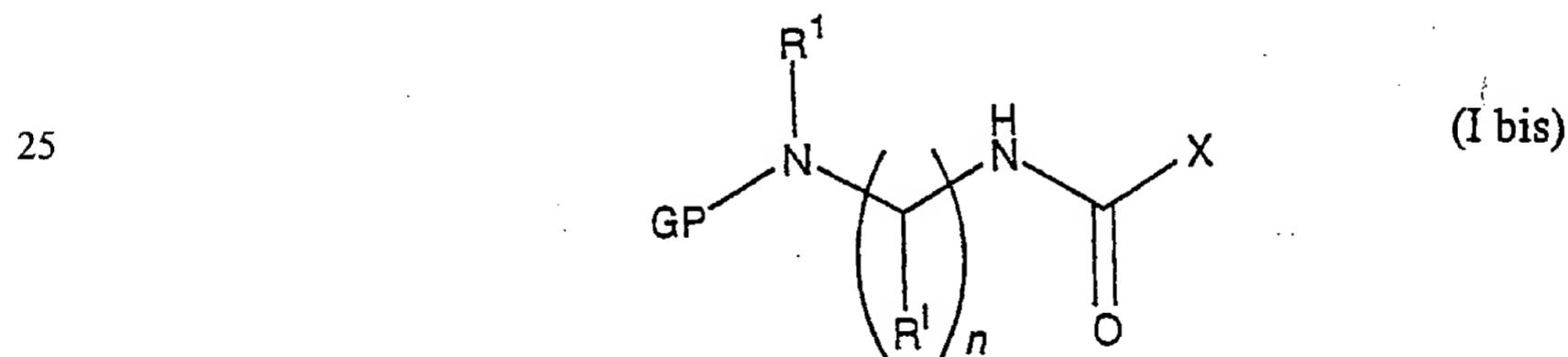
- n=2, GP=Boc, R¹ = isobutyl, R^{2=R'2=R'3=R'3=H}, X = 4-nitrophenol,

- n=2, GP=Boc, R¹ = benzyl, R^{2=R'2=R'3=R'3=H}, X = 4-nitrophenol,

- n=2, GP=Boc, R¹ = CH₂-p-C₆H₄Ot-Bu, R^{2=R'2=R'3=R'3=H}, X = 4-nitrophenol,

- n=2, GP=Boc, R¹ = H, R^{2=R'2=R'3=R'3=H}, X = 4-nitrophenol.

The invention also has for its object compounds of the formula (I bis)

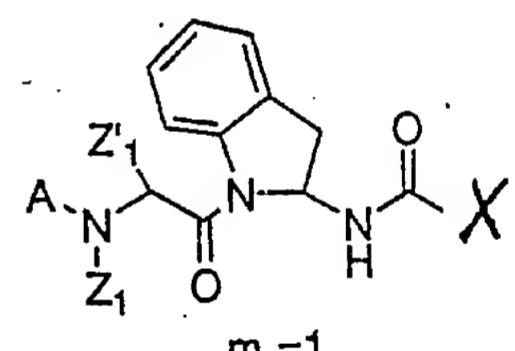
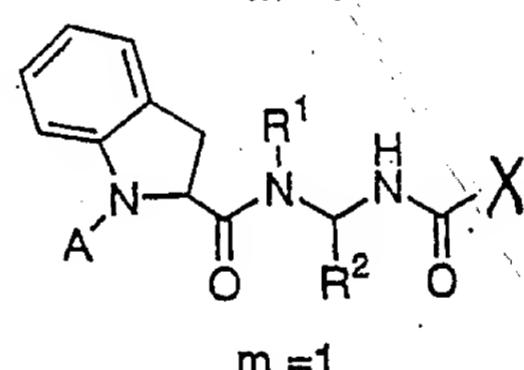
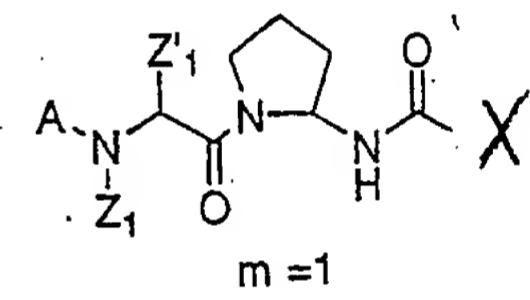
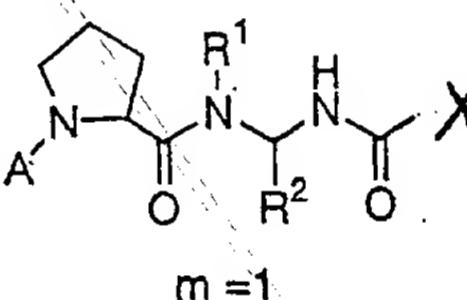
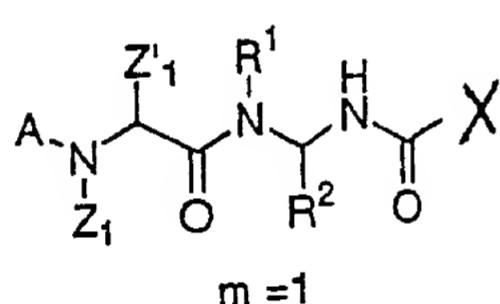
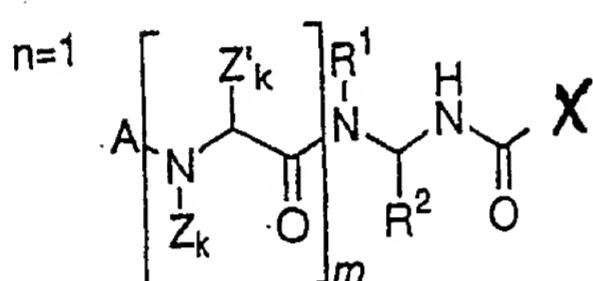


in which n, i, GP, X, R¹ and Rⁱ have the meanings mentioned above, in connection with formula (III bis).

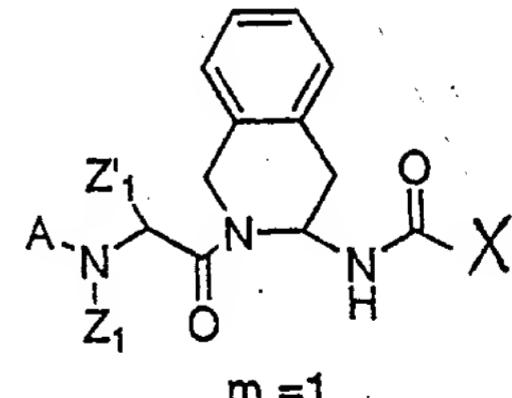
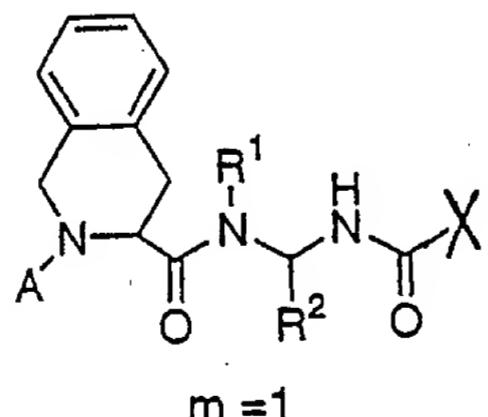
30 A preferred group of compounds of formula (III bis) is constituted by those in which 1 ≤ n ≤ 4, X is as defined above in connection with formula (III bis) and is particularly from p-nitrophenol, N-hydroxysuccinimide,

pentafluorophenol, hydroxy-1,2,3-benzotriazole or
 imidazole, A is an oxycarbonyl or acyl group as defined
 above in connection with formula (III bis),
 and particularly the compounds in which q and m are
 comprised from 1 to 10, and preferably equal from 1 or 2,
 and more particularly those in which A=Boc and Fmoc,
 and in particular the compounds having the following
 formulas:

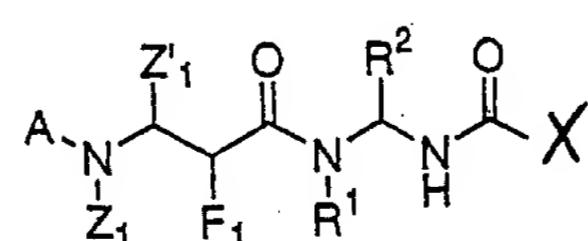
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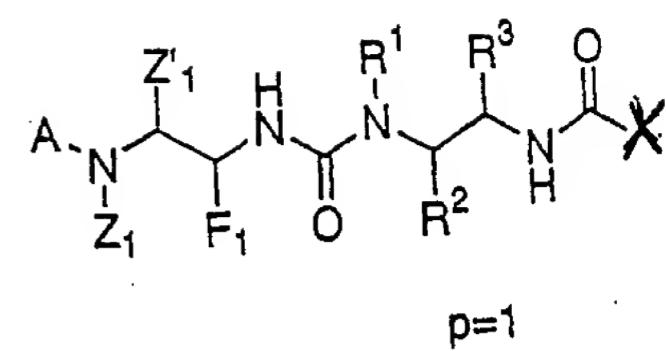
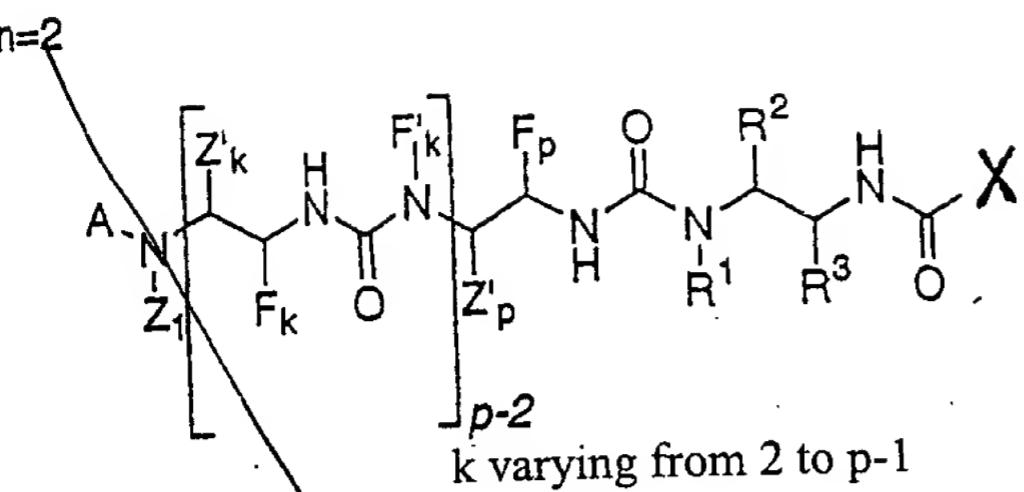


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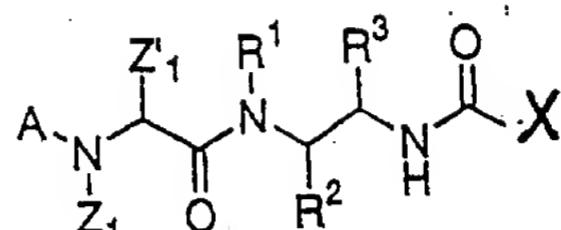


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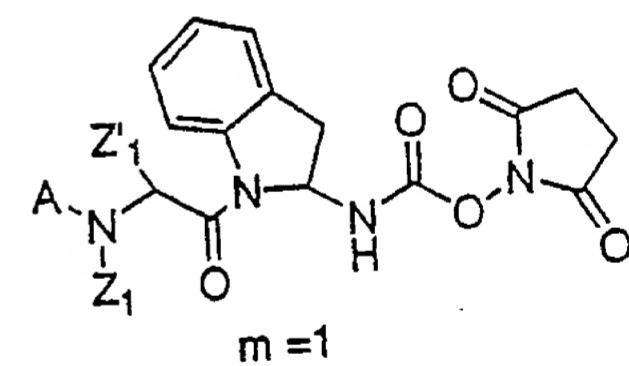
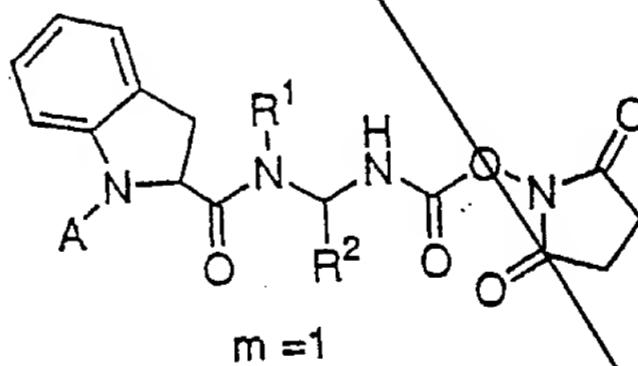
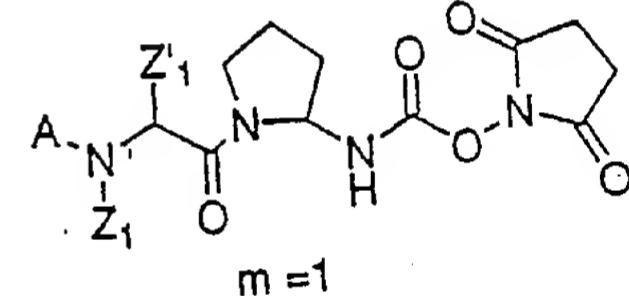
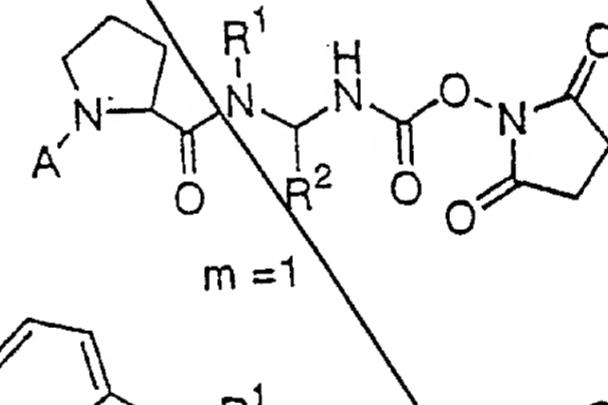
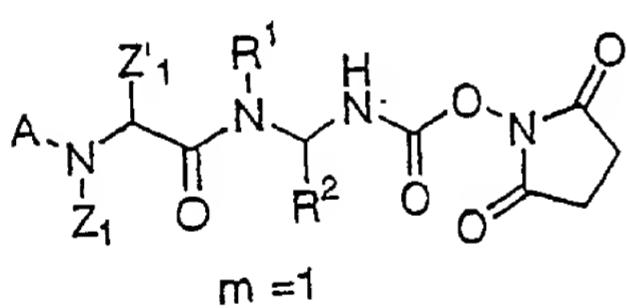
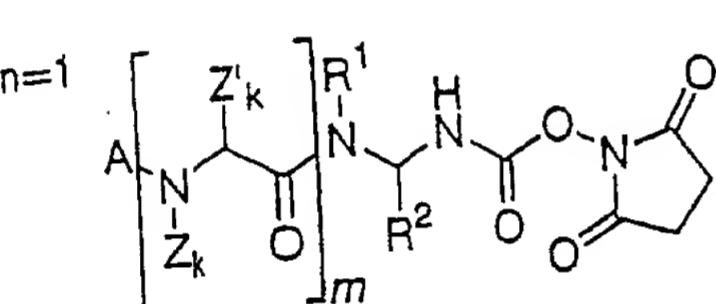
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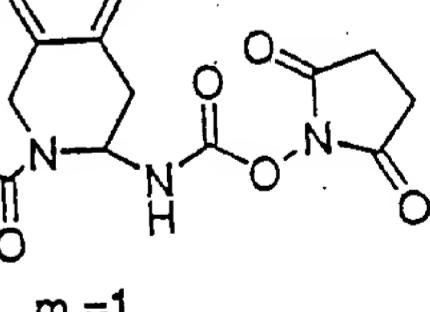
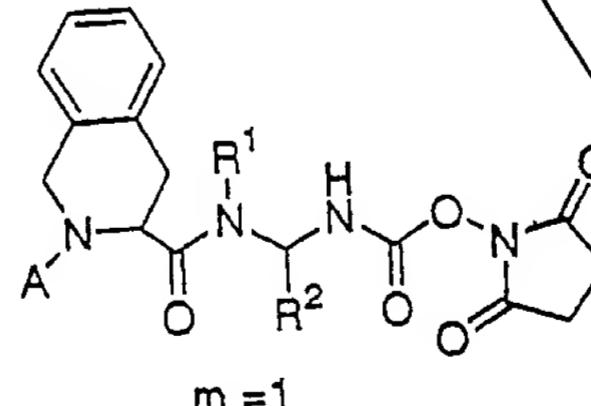
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and more particularly the compounds of the following
formulas:

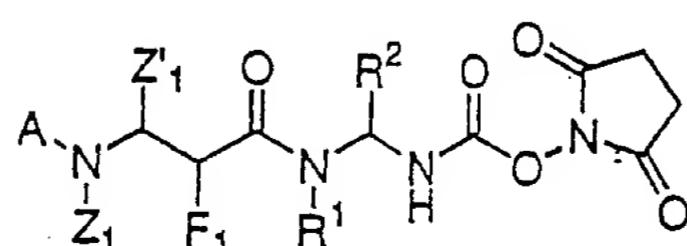
Patent application No. 2,000,000, filed 1970, published 1972



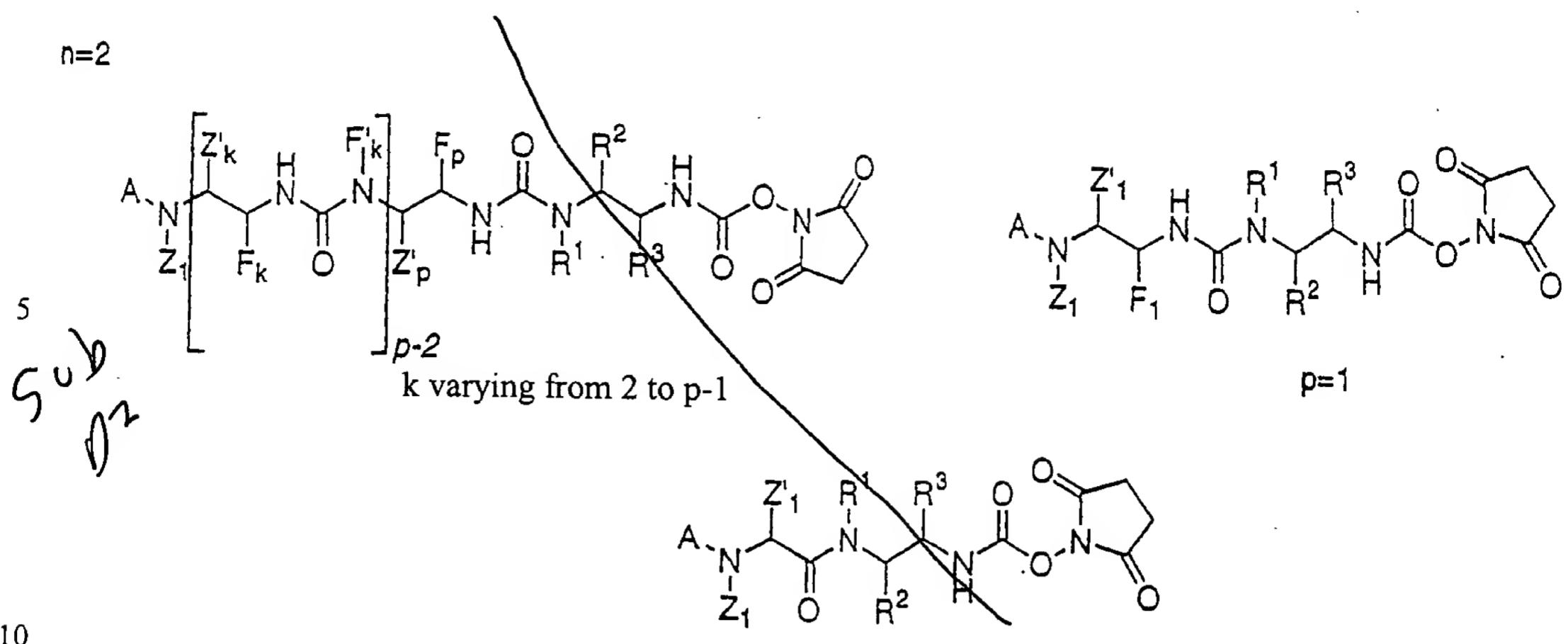
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n=2



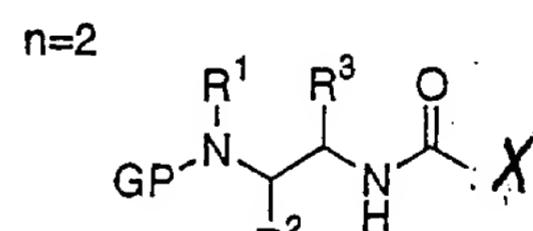
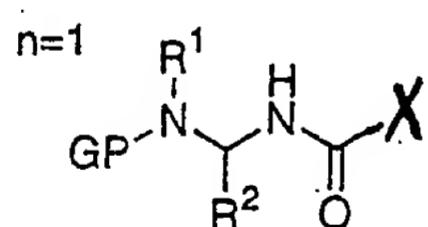
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A preferred group of compounds of formula (I bis) is constituted by those in which $1 \leq n \leq 4$, X is as defined above with respect to formula (III bis) and is particularly from p-nitrophenol, N-hydroxysuccinimide, pentafluorophenol, hydroxy-1,2,3-benzotriazole or imidazole, GP is an oxycarbonyl or acyl group as defined above in connection with formula (III bis),

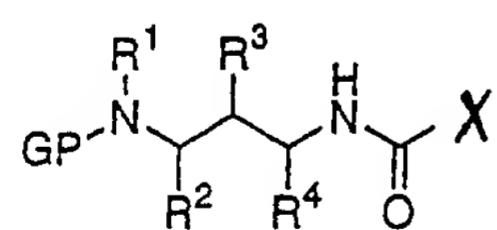
and particular those in which GP is preferably Boc, Fmoc,

and in particular the compounds having the following formulas:

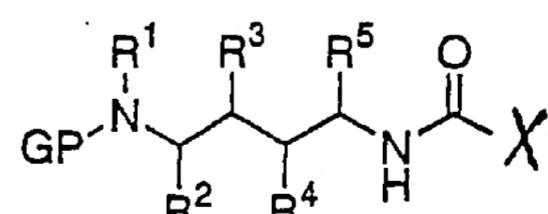
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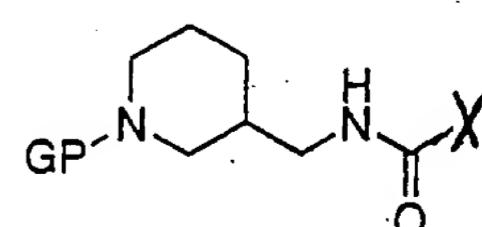
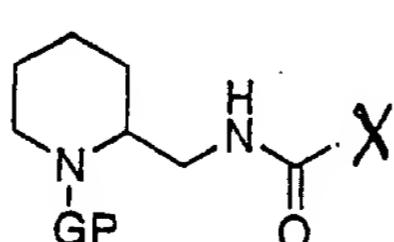
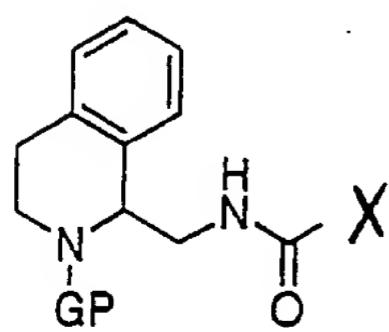
n=3



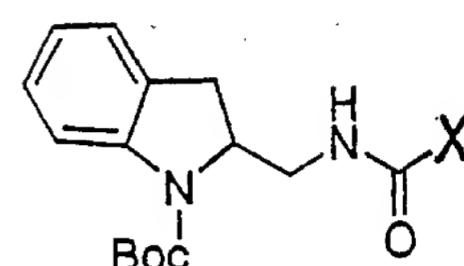
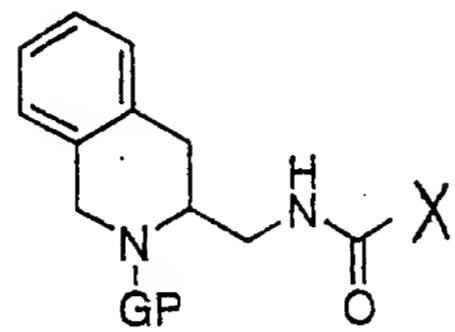
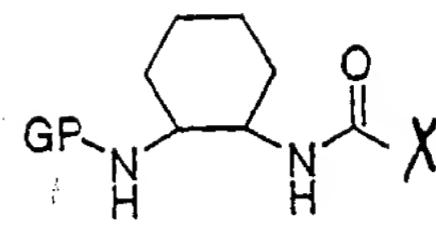
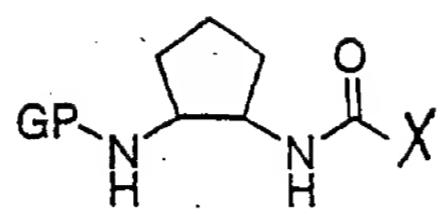
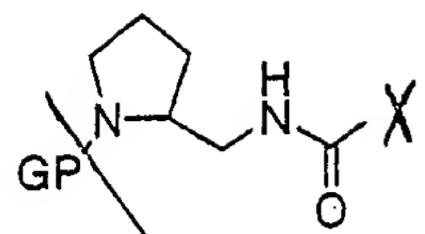
n=4



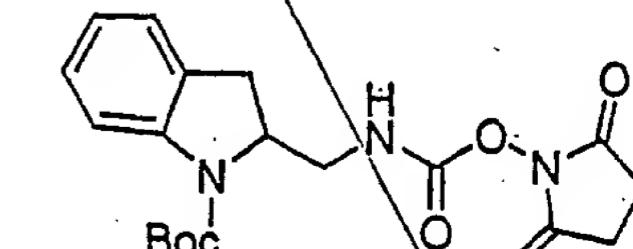
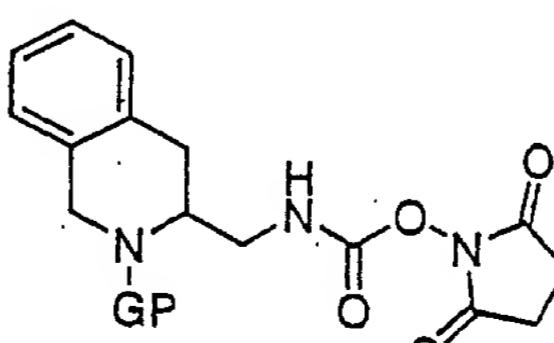
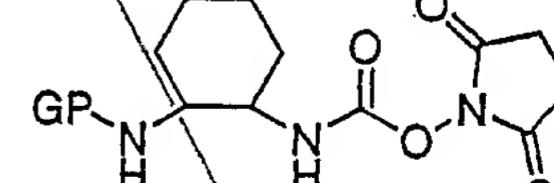
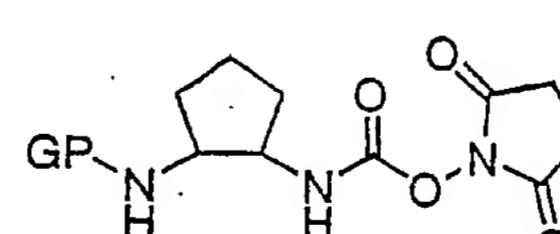
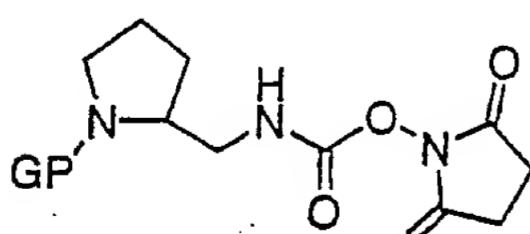
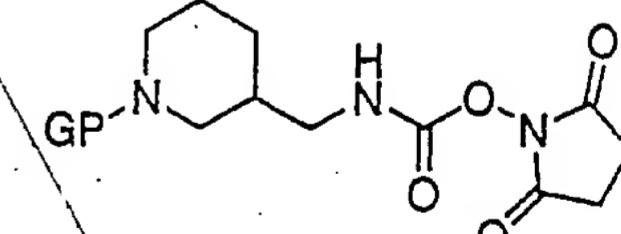
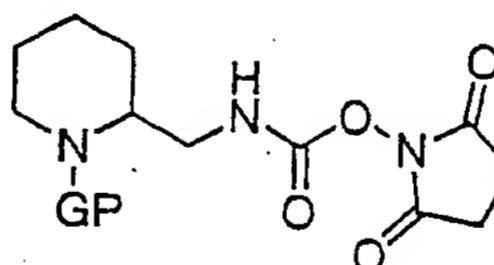
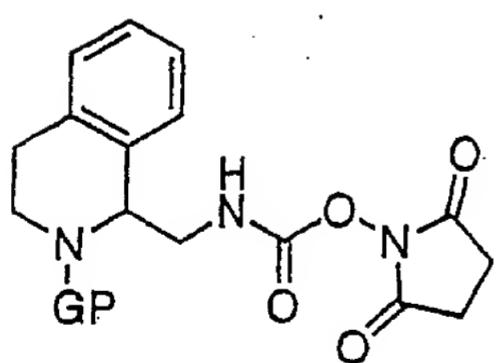
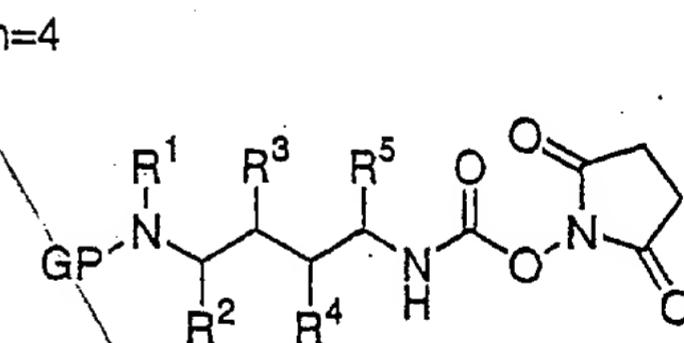
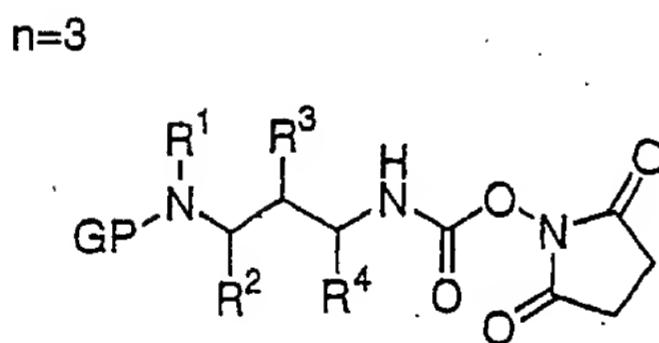
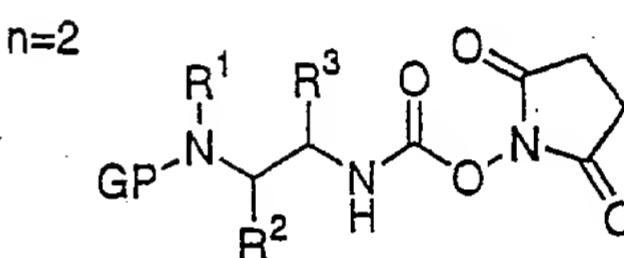
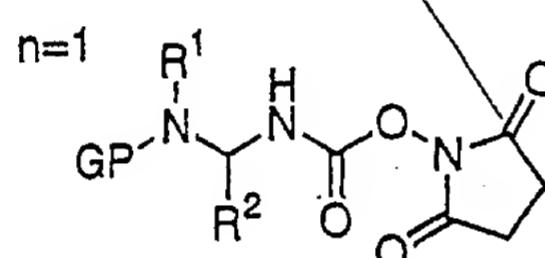
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B³
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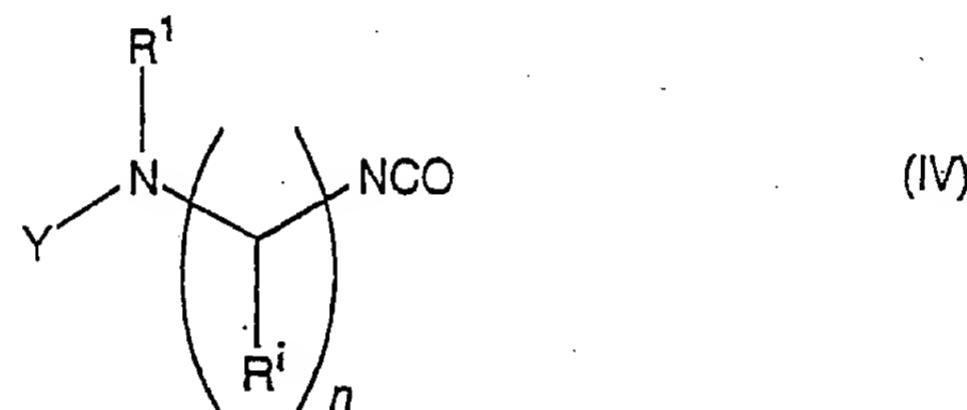
and more particularly the compounds having the following formulas:



The compounds of formulas (III) and (III bis) are activated carbamates analogous to the compounds of formulas (I) and (I bis) in which the protective group is replaced for example by an amino acid chain, a pseudopeptide, or an oligomer of urea. They can be obtained from corresponding isocyanates of formula (IV) defined hereafter.

The compounds of formulas (I) and (I bis) are activated carbamates derived from N-protected amino acids of formula IX defined hereafter and which can be obtained from isocyanates of formula (II) defined hereafter.

The invention also relates to compounds of formula (IV)

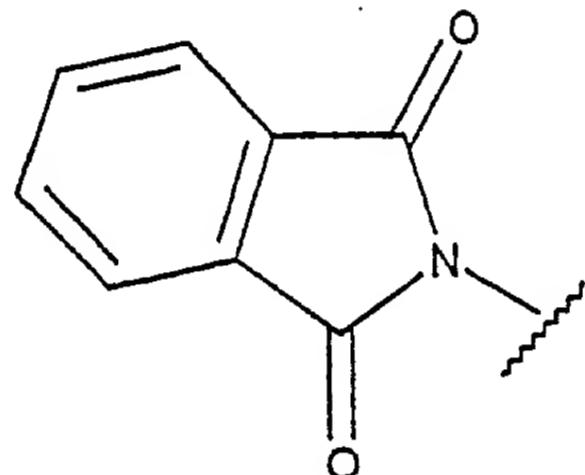


in which

- "n" is a whole number greater than or equal to 1, preferably 1 to 10, preferably 1 to 4,
 - "i" is a whole number varying from 2 to n+1,
 - the Y group can be or contain:
 - 1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)
- A-N(Z₁)-C(Z'₁)(Z''₁)-Ψ₁[*]-C(Z'₂)(Z''₂)-Ψ₂[*]-...-Ψ_{k-1}[*]-C(Z'_k)(Z''_k)-Ψ_k[*]-...
- Ψ_{p-1}[*]C(Z'_p)(Z''_p)-Ψ_p[*]-
- "p" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,
 - "k" is a whole number varying from 1 to p,
 - or A is a group selected from:
 - * hydrogen

- * oxycarbonyl (ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenlymethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),
- 5 * acyl (RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl, aryl,
- * alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,
- * phenyl, particularly aryl,
- 10 * urea (RNHCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl,
- * phthalimide (R₁=Ø)

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SEARCHED
INDEXED
FILED
20



25

- * biotin
 - * the group A can form with the nitrogen atom N to which it is contiguous an "NH₂⁺" entity
 - Z_k, Z'_k and Z''_k can each represent or independently: hydrogen,
 - the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,
 - a (C1-C20) alkyl group, substituted or unsubstituted with one or several substituents from the following:
- 1/ -COOR_b
- 2/ -CONHR_b
- 3/ -COOH
- 4/ -OH, OR_b
- 5/ -NHR_b
- 6/ -NH₂

- 7 / -NH(CO)R_b
- 8 / aryl whose cyclic structure contains 5 to 20
carbon atoms
- 9 / halogen
- 5 10 / carbonyl of 1 to 10 carbon atoms
- 11 / nitrile
- 12 / guanidine
- an aryl group whose cyclic structure contains 5 to 20
halogen atoms
- 10 -OR_b
- COOR_b
- CONHR_b
- CONH₂
- CH₂COOR_b
- CH₂CONHR_b
- CH₂CONH₂
- R_b representing an allyl, benzyl, t-butyl,
fluorenylmethyl, alkyl having 1 to 20 carbon atoms group,
or an aryl group whose cyclic structure contains 5 to 20
carbon atoms,
- -Ψ_k[*] - are independently either peptide linkages CO-
NH, or linkages of different chemical nature selected
particularly from the following list:
- ψ_k[*]- = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ;
-N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ; -CH(F_k)=CH(F_k')- ; -CH₂NH- ; -NHCO- ;
-NHCONH- ; -N(F_k)CON(F_k')- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ;
-CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_k')- ;
-CH₂-CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_k')CONH-
- 30 F_k and F_k' representing, independently from each other,
hydrogen, the protected or unprotected side chain of an
amino acid selected from proteinogenic and non-
proteinogenic amino acids, halogen, an alkyl group of 1 to

20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

5 A-N(Z₁)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-

- "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

10 - "k" is a whole number varying from 1 to m,
- A defined as above,

3/ A GP group which can be:

- a protective group selected from:

* hydrogen

* oxycarbonyl (GP = ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxy-carbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),

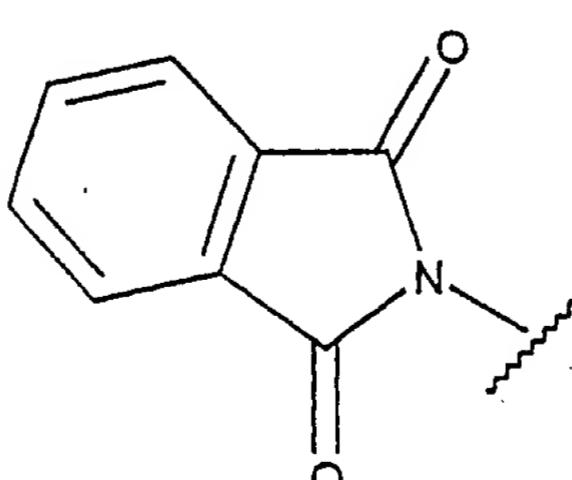
* acyl (GP = RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl, aryl,

* alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,

* phenyl, particularly aryl,

* urea (GP = RNHCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl,

* phthalimide (R¹ = Ø)



* biotin

* O₂ (corresponds to a nitro group as the masked form of the amine), R¹=Ø

- the GP group which can also be such that the GP-N entity forms an "NH₂⁺" entity

5 - the R¹, Rⁱ and R groups can each represent independently of each other:

hydrogen

halogen

10 the protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents selected from:

1/ -COOR_a

2/ -CONHR_a

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH₂

8/ -NH(CO)R_a

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

25 11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

an NH₂ group

an OH group

-COOR_a

-CONHR_a

-CONH₂

-CH₂COOR_a

-CH₂CONHR_a

5 -CH₂CONH₂

R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

10

the compound of formula (IV) having the following property:

- if one or several asymmetric carbons are present in the formula (IV), then their configuration can be independently either D (dextro) or L (levo),

- the groups R¹ and Rⁱ can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between Rⁱ and R^{i+kc} (where kc is a positive integer, preferably comprised between 1 to 3)

2/ cyclization between R¹ and Rⁱ wherein preferably i = 2, 3 or 4.

25

- provided that the compound of formula (IV) be different from the compounds in which:

- n=1, GP=Boc or benzyloxycarbonyl, R₁ = Ø

- n=2, GP=phtalimide, R₁ = Ø, R₃=benzyle, R'₂=R₂=R'₃=H

- n=2, GP=phtalimide, R₁ = Ø, R₃=methyle, R'₂=R₂=R'₃=H

- n=2, GP=phtalimide, R₁ = Ø, R₃=H, R'₂=R₂=R'₃=H

- n=2, GP=phtalimide, R₁ = Ø, R₃=CH₂i-Pr, R'₂=R₂=R'₃=H

- n=2, GP=phtalimide, R₁ = Ø, R₃=CH₂COOt-Bu, R'₂=R₂=R'₃=H

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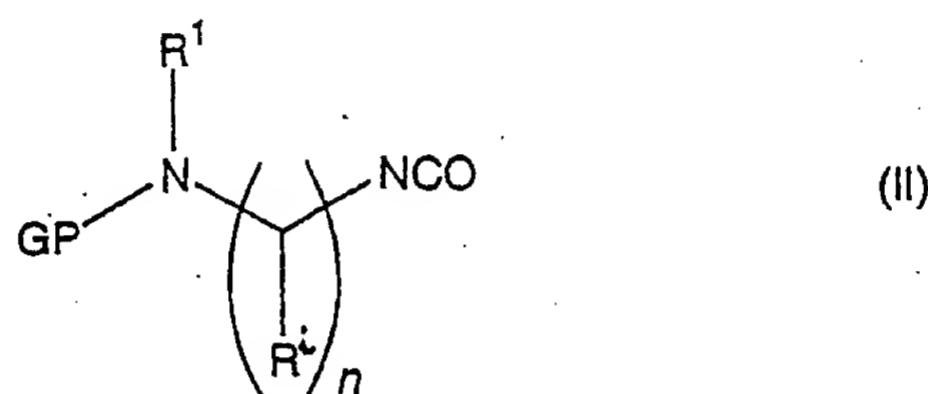
- n=2, GP=phtalimide, R₁ = Ø, R₃=CH₂CH₂CH₂NHBoc, R'₂=R₂=R'₃=H

R'₂=R₂=R'₃=H

- n=2, GP=phtalimide, R₁ = Ø, R₃= CH₂ CH₂ CH₂NHCNH(N-Mtr), R'₂=R₂=R'₃=H, (Mtr =4-methoxy-2,3,6-trimethyl-benzene-sulphonyl)
- 5 - n=2, GP=Boc, R₁ = benzyl, R₂=R'₂=R₃=R'₃=H
- n=2, GP=Boc, R₁ = i-Bu, R₂=R'₂=R₃=R'₃=H
- n=2, GP=Boc, R₁ = H, R₂=R'₂=R₃=R'₃=H

The invention also has for its object compounds of the formula (II)

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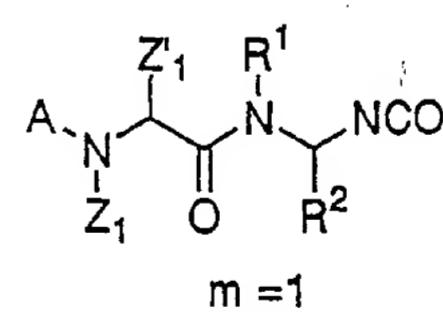
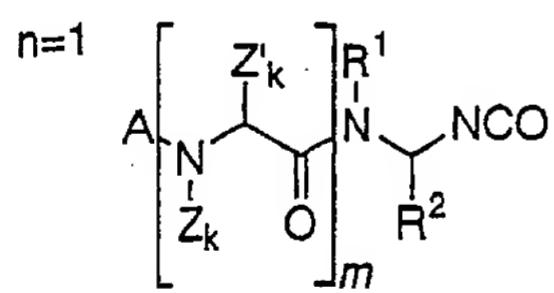
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in which n, i, GP, R¹ and Rⁱ have the meanings mentioned above in connection with formula (IV).

A group of preferred compounds of formula (IV) are those in which 1 ≤ n ≤ 4, A is an oxycarbonyl or acyl group as defined above in connection with formula (IV),

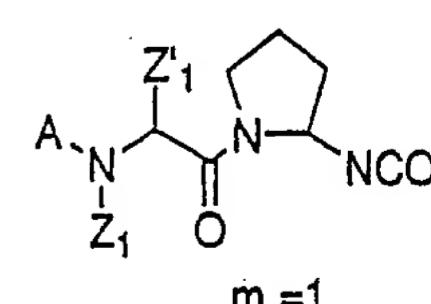
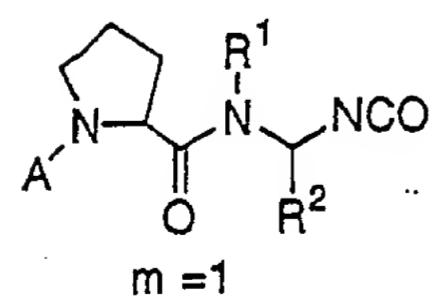
and particularly the following compounds for which p and m are comprised from 1 to 10 and preferably equal to 1 or 2, and particularly those for which A = Boc and Fmoc,

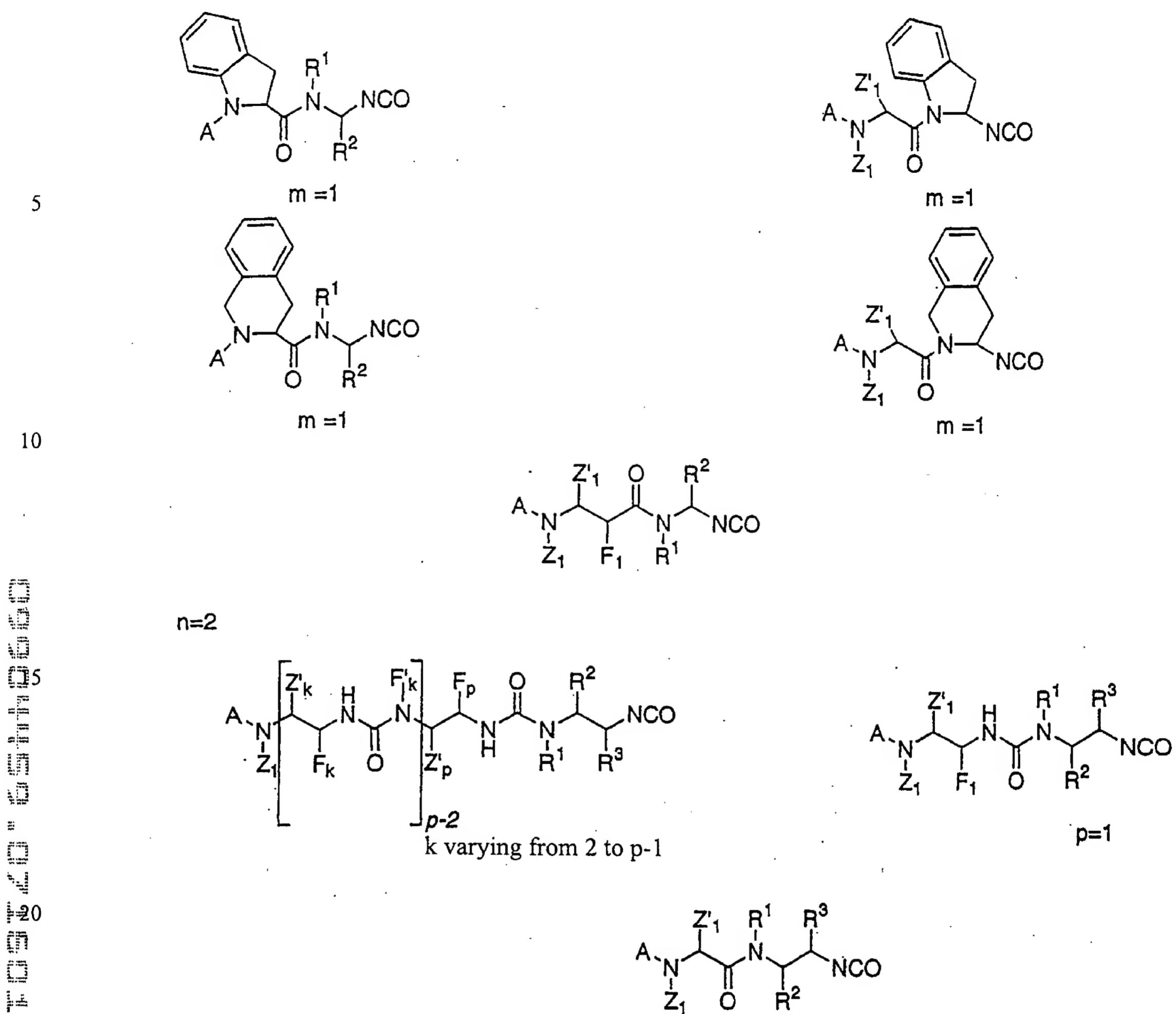
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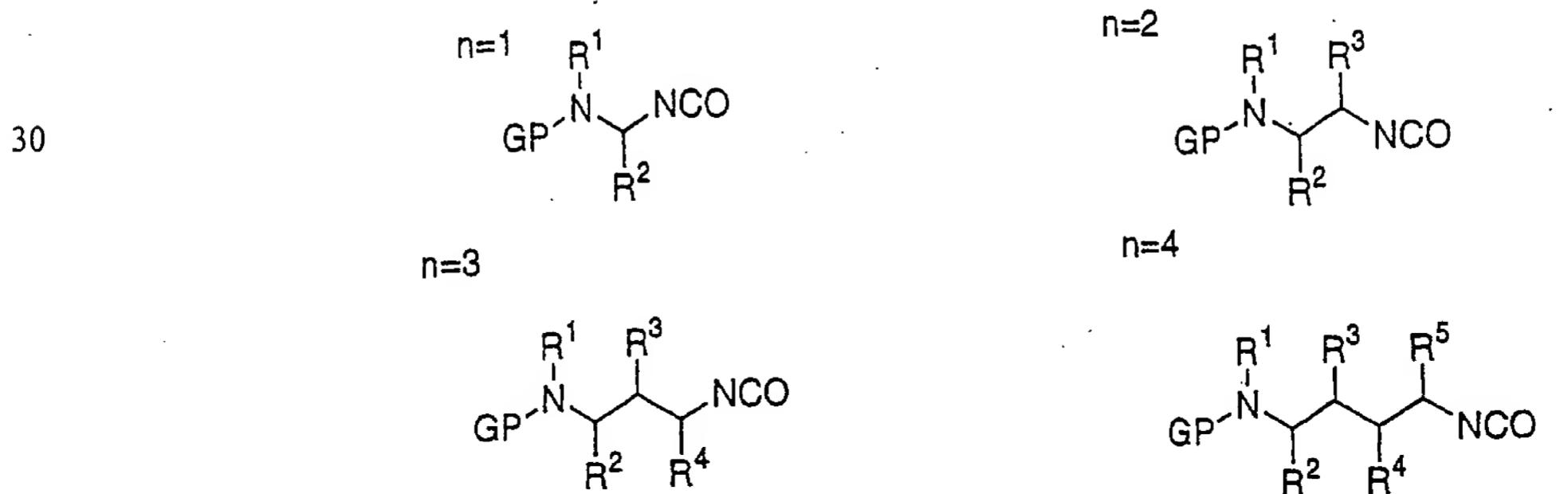
A different from Boc
(tertbutoxycarbonyle) and benzyloxycarbonyle

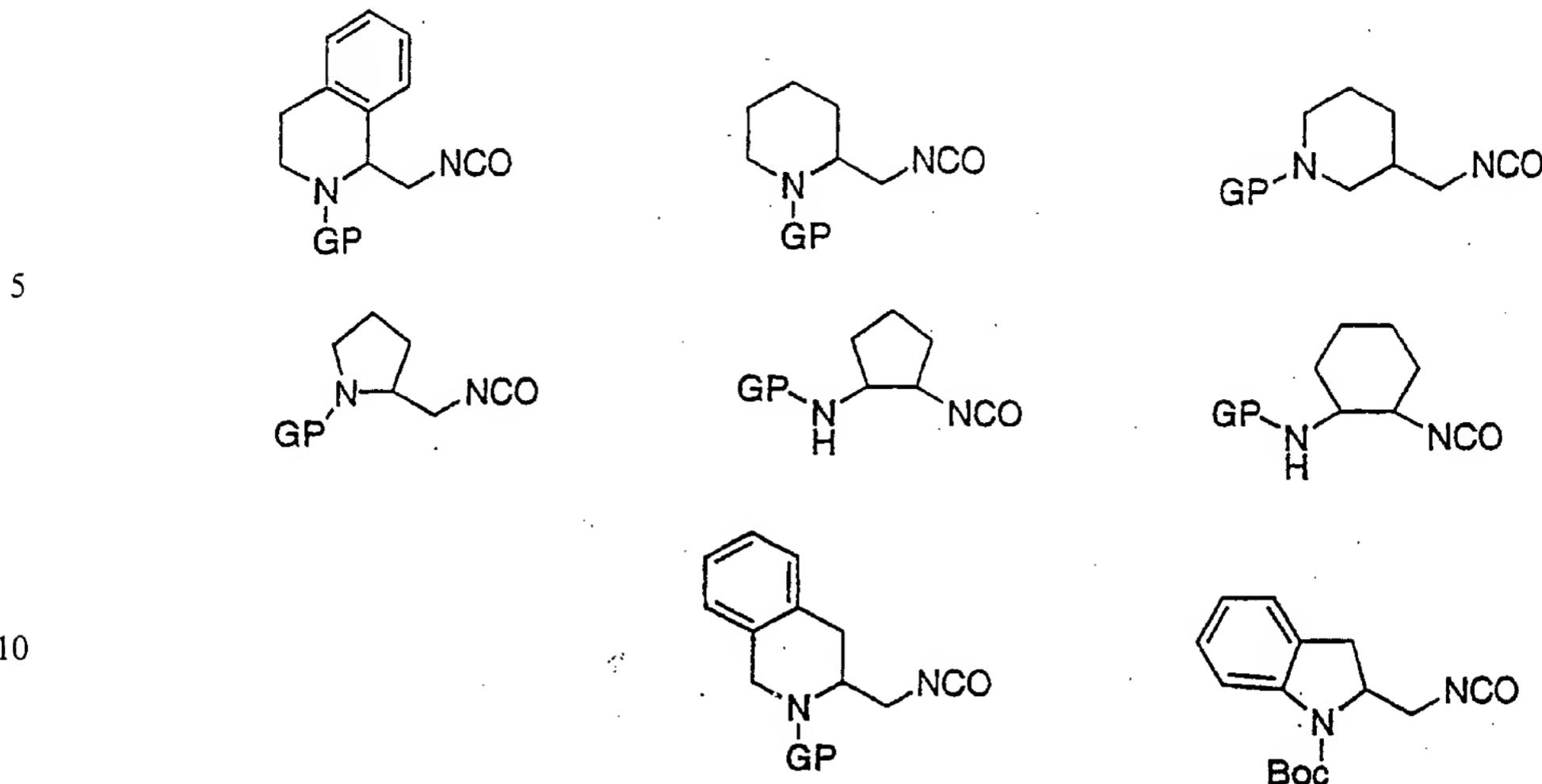
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A preferred group of compounds of formula (II) are those in which $1 \leq n \leq 4$, GP is an oxycarbonyl or acyl group as defined above with respect to formula (IV), and particularly the following compounds, in particular those in which GP=Boc and Fmoc,

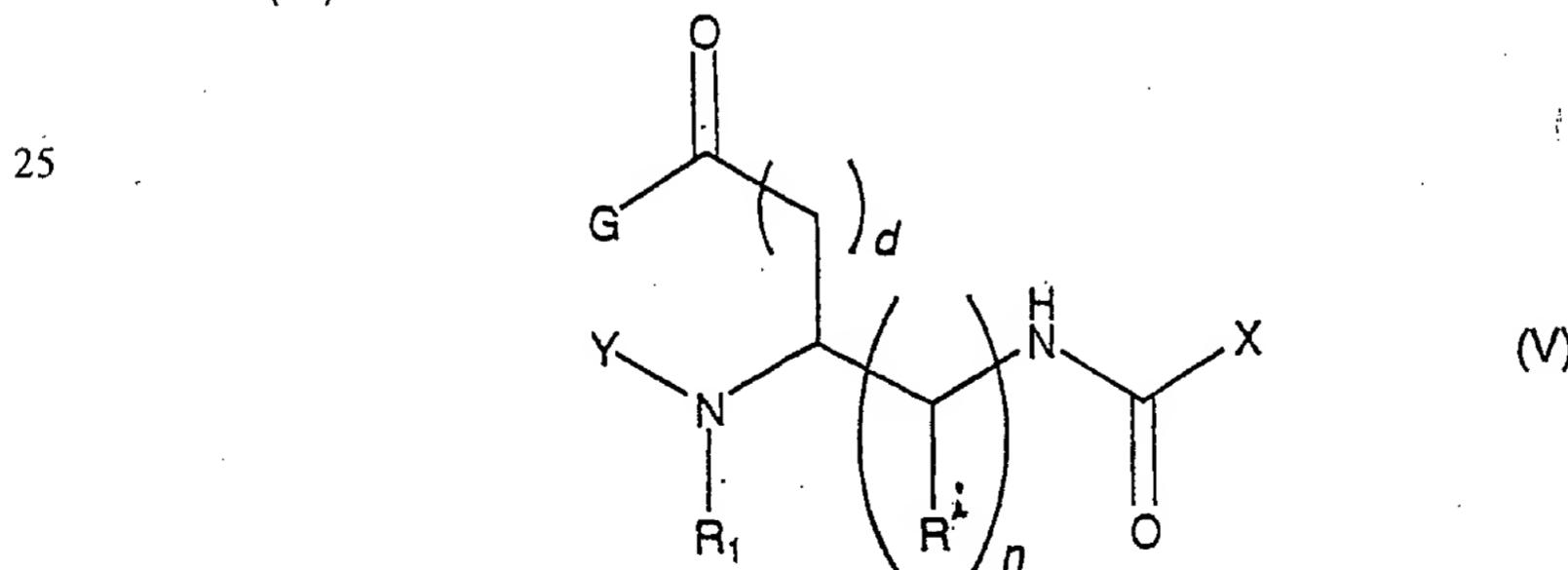




The isocyanates of formula (IV) can be used as precursors for the synthesis of the compounds of formula (III) and (III bis) and can be obtained from compounds of the formula (X) defined hereinafter.

The isocyanates of formula (II) are the precursors used in the synthesis of compounds of formulas (I) and (I bis) and can be obtained from N-protected amino acid derivatives of formula (IX) defined hereafter.

The invention also relates to compounds of the formula (V)



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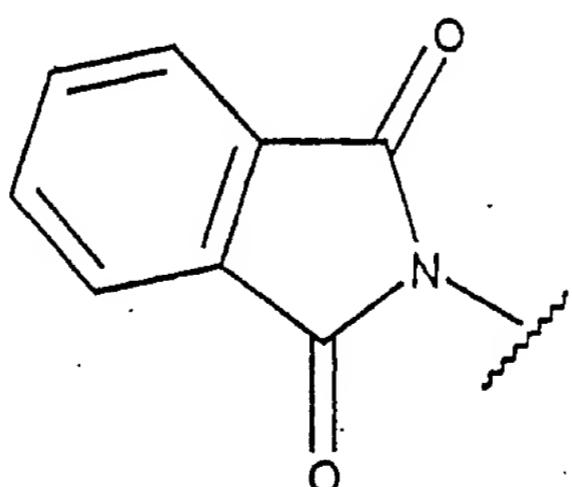
in which

- "n" is a whole number greater than or equal to 1, particularly from 1 to 4 and preferably from 1 to 2,

- "d" is a whole number comprised between 0 and 4, preferably equaling 0 or 1,
- "i" is a number varying from 2 to n+1,
- 5 - the Y group can be or contain:
 - 1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

A-N(Z₁)-C(Z'₁)(Z''₁)-Ψ₁[*]-...-Ψ_{k-1}[*]-C(Z'_k)(Z''_k)-Ψ_k[*]-...Ψ_{p-1}[*]C(Z'_p)(Z''_p)-Ψ_p[*]-
- 10 - "p" is a whole number greater than or equal to 1, preferably from 1 to 50; preferably from 1 to 10,
 - "k" is a whole number varying from 1 to m,
 - A is a group selected from:
 - * hydrogen
 - * oxycarbonyl (ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),
 - * acyl (RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl, aryl,
 - * alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,
 - * phenyl, particularly aryl,
 - * urea (RNHCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl,
 - * phthalimide (R¹=Ø)
- 25

30



* biotin

* the group A can form with the nitrogen atom N with which it is contiguous an "NH₂⁺" entity

5 - Z_k, Z'_k, and Z''_k can each represent and independently of one another:

hydrogen,

the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

10 a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -COOR_b

2/ -CONHR_b

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH₂

7/ -NH(CO)R_b

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

25 an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-COOR_b

30 -CONHR_b

-CONH₂

-CH₂COOR_b

-CH₂CONHR_b

-CH₂CONH₂

R_b representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

5 - Ψ_k^* - are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

10 Ψ_k^* = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ;
 -N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ; -CH(F_k)=CH(F_k')- ; -CH₂NH- ; -NHCO- ;
 -NHCONH- ; -N(F_k)CON(F_k')- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ;
 -CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_k')- ;
 -CH₂-CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_k')CONH-

F_k and F_k' representing, independently of each other, hydrogen, the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, halogen, an alkyl of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

20 2/ an amino acid residue or an amino acid chain:

A-N(Z_1)-C(Z'_1)(Z''_1)-CO-N(Z_2)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-

25 - "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

25 - "k" is a whole number varying from 1 to m,
 - A defined as above,
 - the R^1 , R^i , and R groups can each represent independently of each other:

hydrogen,

30 halogen,

the protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids,

a (C₁-C₂₀) alkyl group, unsubstituted or substituted with one or several substituents from the following:

- 15
20
25
- 1/ -COOR_a
 - 2/ -CONHR_a
 - 3/ -COOH
 - 4/ -OH
 - 5/ -OR_a
 - 6/ -NHR_a
 - 7/ -NH₂
 - 8/ -NH(CO)R_a
 - 9/ aryl
 - 10/ halogen
 - 11/ carbonyl of 1 to 10 carbon atoms
 - 12/ nitrile
 - 13/ guanidine
 - 14/ nitro
 - an aryl group, whose cyclic structure contains 5 to 20 carbon atoms
 - an OR_a group
 - an NH₂ group
 - an OH group
 - COOR_a
 - CONHR_a
 - CONH₂
 - CH₂COOR_a
 - CH₂CONHR_a
 - CH₂CONH₂
 - R_a representing an allyl, benzyl, t-butyl, fluorenethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,
- 30

- the G group can be or contain:

A/ an amino acid residue or an amino acid residue

chain:

-N(S₁)C(S'₁)(S''₁)-CO-N(S₂)-...-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-...CO-

5 N(S_v)-C(S'_v)(S''_v)-CO-D

- "v" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10 with preferably v>3 and v>5,

10 - D can be:

-NH₂

-NHCOR_c

-NHR_c

-NR_cR_d

-N(R_c)CON(R_d)

-OH

-OR_c

15 R_c and R_d represent independently of each other an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- S_k, S'_k and S''_k can each represent independently:

hydrogen,

20 the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

25 a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -COOR_e

30 2/ -CONHRE

3/ -COOH

4/ -OH, OR_e

5/ -NHR_e

6/ -NH₂

- 7/ $-\text{NH}(\text{CO})\text{R}_e$
- 8/ aryl whose cyclic structure contains 5 to 20 carbon atoms
- 9/ halogen.
- 5 10/ carbonyl
- 11/ nitrile
- 12/ guanidine
- an aryl group whose structure contains 5 to 20 carbon atoms
- 10 an OR_e group
- an NH_2 group
- an OH group
- a halogen
- R_e representing an allyl, benzyl, t-butyl, fluorenethylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.
- B/ a radical selected from:
- * NH_2
- * O-benzyl
- * O-allyl
- * O-methyl
- * O-ethyl
- * O-terbutyl

- the X group represents a group giving to the compound of formula (V) an activated molecular structure adapted to react with alcohols or amines to form carbamic acid derivatives or ureas, and is particularly derived from a compound selected from phenols, if desired substituted with nitro or a halogen or hydroxylamine derivatives and more particularly selected from:

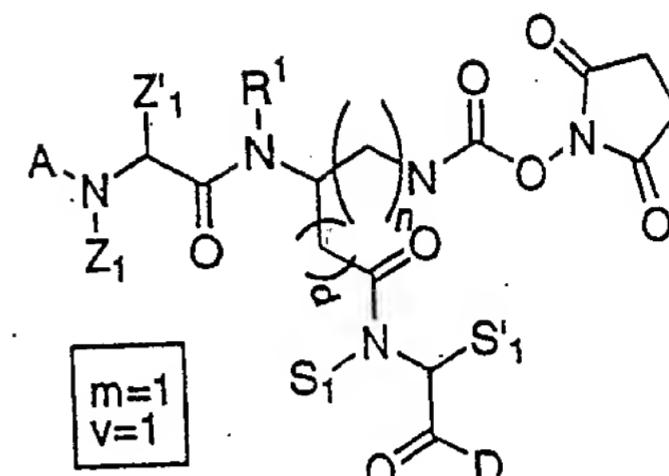
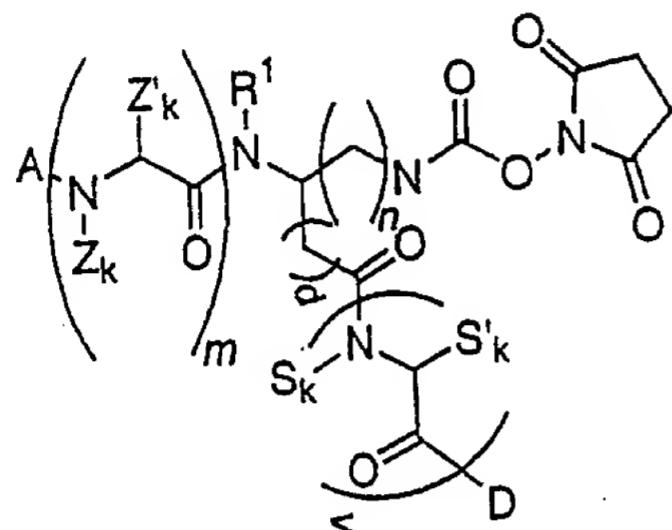
- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- 5 - p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 10 - 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)
- imidazole
- tetrazole

the compounds of formula (V) having the following property:

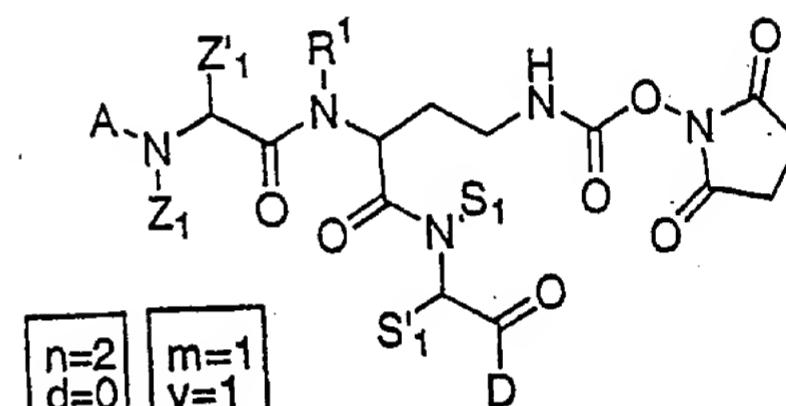
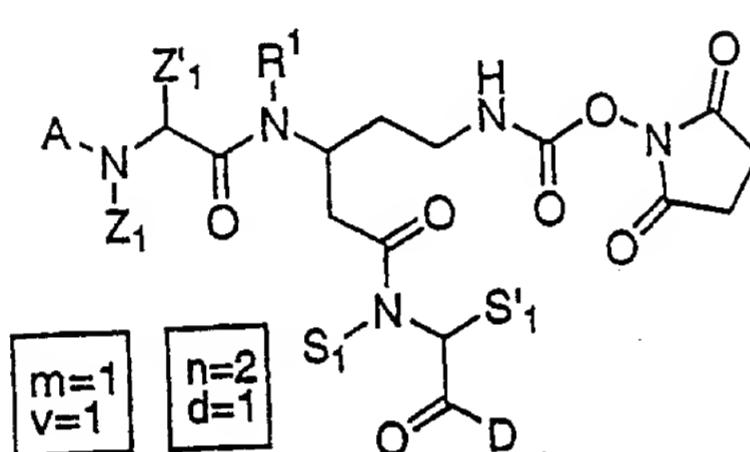
- if one or several asymmetric carbons are present in formula (V), then their configuration can be in independent manner either D (dextro) or L (levo),
 - the groups R^1 and R^i groups can also be defined on the basis of intramolecular cyclizations which are the following:
- 25 1/ cyclization between R^i and R^{i+kc} (in which kc is a positive whole number, preferably comprised between 1 and 3)
- 2/ cyclization between R^1 and R^i wherein preferably $i=2, 3$ or 4 ,
- 30 and more particularly the compounds corresponding to formula (V) in which $1 \leq n \leq 4$, $d = 0$ or 1 , $X = N$ -hydroxysuccinimide, A is an oxycarbonyl or acyl group, and particularly the compounds in which p , m and v are

comprised from 1 to 10 and preferably equal to 1 or 2, and
preferably those in which A = Boc and Fmoc,
and particularly the compounds of the following
formulas:

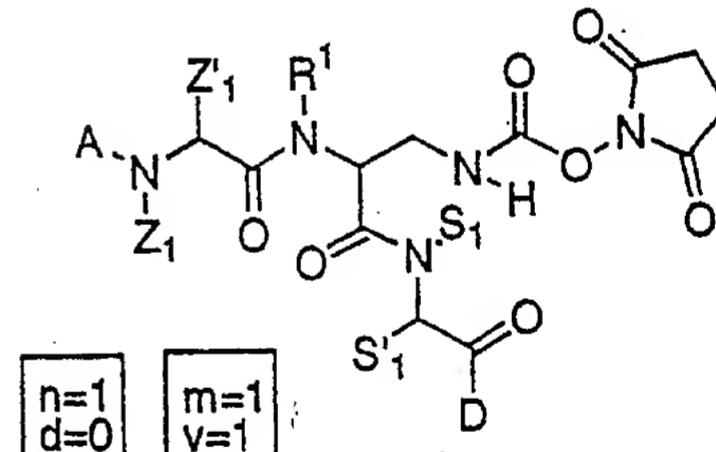
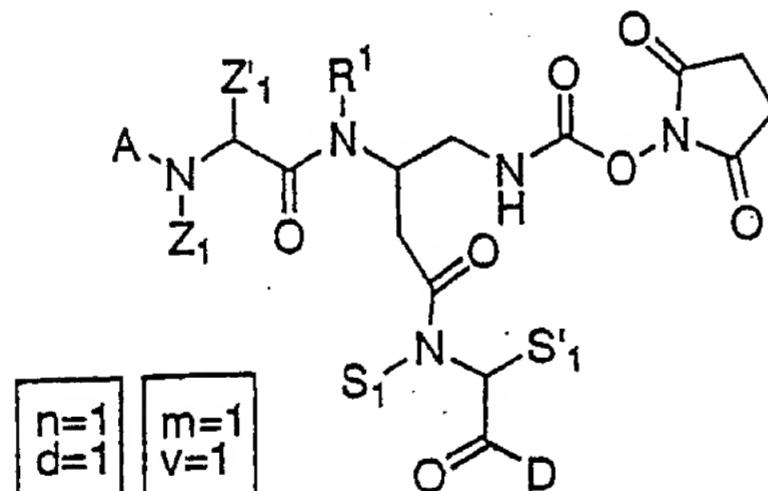
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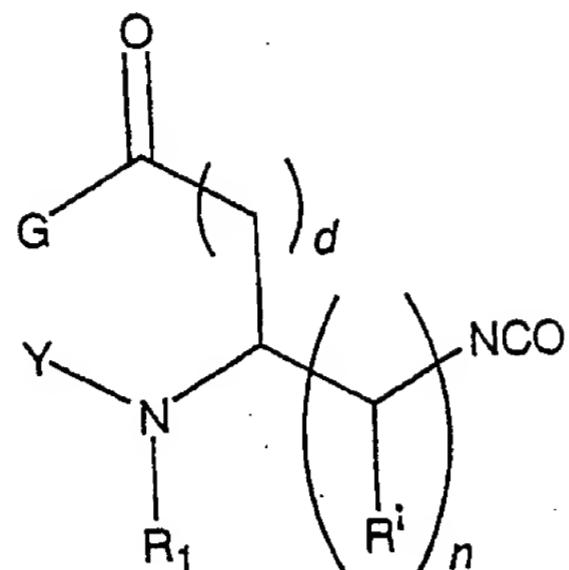
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The compounds of formula (V) are activated carbamates
analogous to compounds of formulas (I) and (I bis) in which
the activated carbamate is introduced into the side chain
of a protective amino acid or a peptide, a pseudopeptide or
else an oligomer of urea.

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The invention also relates to compounds of formula
(Vbis)

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(Vbis)

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in which

- "n" is a whole number greater than or equal to 1, comprised particularly by 1 to 4, and preferably 1 to 2,

- "d" is a whole number comprised from 0 to 4, preferably equaling 0 or 1,

- "i" is a whole parameter greater than or equal to 2 defined in the following manner: i takes all the whole values comprised from 2 to n+1,

20

- the Y group can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

A-N(Z₁)-C(Z'₁)(Z''₁)-Ψ₁[*]-...-Ψ_{k-1}[*]-C(Z'_k)(Z''_k)-Ψ_k[*]-...-Ψ_{p-1}[*]C(Z'_p)(Z''_p)-Ψ_p[*]-

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- "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

- "k" is a whole number varying from 1 to p,

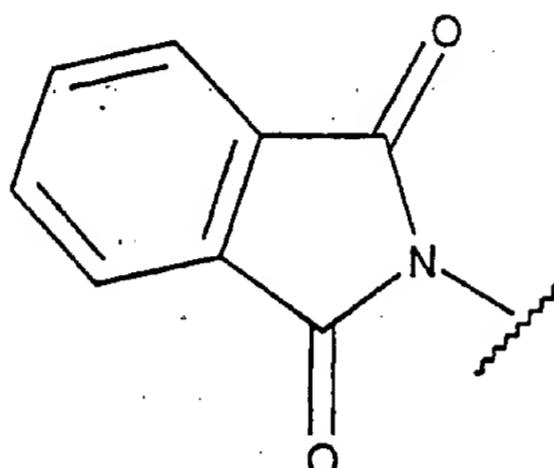
- A is a group selected from:

* hydrogen

* oxycarbonyl (ROCO), preferably Boc (R = C(CH₃)₃), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH₂Ph), allyloxycarbonyl (R = -CH₂CH=CH₂),

* acyl (RCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl, aryl,

- * alkyl (R), preferably R = trityl, CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, benzyl, allyl,
- * phenyl, particularly aryl,
- * urea (RNHCO), preferably R = CH₃, CH₂CH₃, CH(CH₃)₂, C(CH₃)₃, phenyl, benzyl, allyl,
- * phthalimide (R¹=Ø)



- * biotin
 - * the A group can form with the nitrogen atom N to which it is contiguous an "NH₂" entity,
 - or Z_k, Z'_k, and Z''_k can each represent and independently of each other:
 - hydrogen,
 - the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,
 - a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:
- | | |
|----|---|
| 25 | 1/ -COOR _b |
| | 2/ -CONHR _b |
| | 3/ -COOH |
| | 4/ -OH, OR _b |
| | 5/ -NHR _b |
| 30 | 6/ -NH ₂ |
| | 7/ -NH(CO)R _b |
| | 8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms |

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

5 an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-COOR_b

10 -CONHR_b

-CONH₂

-CH₂COOR_b

-CH₂CONHR_b

-CH₂CONH₂

R_b representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- -Ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

ψ_k[*]- = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ; -N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ; -CH(F_k)=CH(F_{k'})- ; -CH₂NH- ; -NHCO- ; -NHCONH- ; -N(F_k)CON(F_{k'})- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ; -CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_{k'})- ; -CH₂-CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_{k'})CONH-

25

30

F_k and F_{k'} representing, independently of each other, hydrogen, the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

A-N(Z₁)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-

N(Z_m)-C(Z'_m)(Z''_m)-CO-

- "m" is a whole number greater than or equal to 1,

5 preferably 1 to 50, preferably 1 to 10,

- "k" is a whole number varying from 1 to m,

- A defined as above

10 - the R¹, R¹ and R groups can each represent independently of each other:

hydrogen,

halogen,

the protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids,

15 a (C₁-C₂₀) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -COOR_a

2/ -CONHR_a

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH₂

8/ -NH(CO)R_a

25 9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

30 13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

an NH₂ group

an OH group

-COOR_a

-CONHR_a

5 -CONH₂

-CH₂COOR_a

-CH₂CONHR_a

-CH₂CONH₂

R_a representing an allyl, benzyl, t-butyl,
10 fluorenylmethyl, alkyl having 1 to 20 carbon atoms group,
or an aryl group whose cyclic structure contains 5 to 20
carbon atoms,

- the group G can be or contain

A/ an amino acid residue or a chain of amino acid residues:

-N(S₁)C(S'₁)(S''₁)-CO-N(S₂)-...-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-...CO-N(S_v)-C(S'_v)(S''_v)-CO-D

- "v" is a whole number greater than or equal to 1,
20 preferably 1 to 50, preferably 1 to 10 and preferably v>3
and v>5,

- "k" is a whole number varying from 1 to v, preferably
1 to 50,

- D can be:

25 -NH₂

-NHCOR

-NHR_c

-NR_cR_d

-N(R_c)CON(R_d)

30 -OH

-OR_c

R_c and R_d represent independently of each other an
allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to

20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

5 - S_k , S'_k and S''_k can each represent independently of each other:

hydrogen,

the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

10 a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ $-COOH$

4/ $-OH$

5/ $-NHR_e$

6/ $-NH_2$

7/ $-NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20
20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

25 an aryl group, whose cyclic structure contains 5 to 20
carbon atoms

an OR_e group

an NH_2 group

an OH group

30 a halogen

R_e representing an allyl, benzyl, t-butyl,
fluorenylmethyl, alkyl having 1 to 20 carbon atoms group,
or an aryl group whose cyclic structure contains 5 to 20
carbon atoms

B/ a radical selected from:

- * NH₂
- * O-benzyl
- * O-allyl
- * O-methyl
- * O-ethyl
- * O-terbutyl

5

the compounds of formula (Vbis) having the following property:

10

- if one or several asymmetric carbon atoms are present in formula (V), then their configuration can be independently of each other either D (dextro) or L (levo),
- the groups R¹ and Rⁱ can also be defined on the basis of intramolecular cyclizations as follows:

15
15
20
20

1/ cyclization between R¹ and R^{i+kc} (wherein kc is a positive whole number, preferably comprised between 1 and 3)

2/ cyclization between R¹ and Rⁱ wherein preferably i = 2, 3 or 4,

25

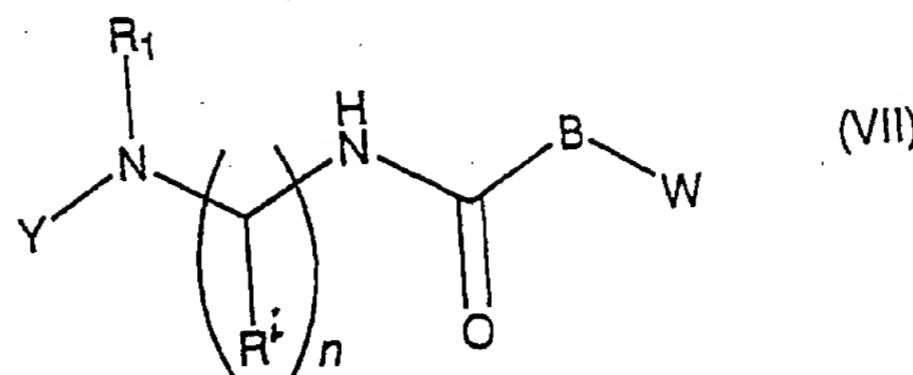
and more particularly the compounds responding to the formula (Vbis) in which 1 ≤ n ≤ 4, d = 0 or 1, X=N-hydroxysuccinimide, A is an oxycarbonyl or acyl group, and particular the compounds in which p, m and v are comprised from 1 to 10 and preferably equal to 1 or 2, and preferably those in which A = Boc and Fmoc.

The isocyanates of formula (Vbis) can be used as precursors for the synthesis of compounds of formula (V) and can be obtained from compounds (XI).

30

The invention also comprises compounds of the formula
 (VII)

5



(VII)

in which

- "n" is a whole number greater than or equal to 1,
 preferably 1 to 50, preferably 1 to 10,
- "i" is a whole number varying from 2 to $n+1$,

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- the Y group can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A-N(Z_1)-C(Z'_1)(Z''_1)-\Psi_1[*]-C(Z'_2)(Z''_2)-\Psi_2[*]-\dots-\Psi_{k-1}[*]-C(Z'_k)(Z''_k)-\Psi_k[*]-\dots$
 $\Psi_{p-1}[*]C(Z'_p)(Z''_p)-\Psi_p[*]-$

- "p" is a whole number greater than or equal to 1,
 preferably 1 to 50, preferably 1 to 10,

- "k" is a whole number varying from 1 to p ,

- or A is a group selected from:

* hydrogen

* oxycarbonyl ($ROCO$), preferably Boc ($R = C(CH_3)_3$),

25 $Fmoc$ (fluorenylmethoxycarbonyl), $benzyloxycarbonyl$ ($R = CH_2Ph$), $allyloxycarbonyl$ ($R = -CH_2CH=CH_2$),

* acyl (RCO), preferably $R = CH_3, CH_2CH_3, CH(CH_3)_2, C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

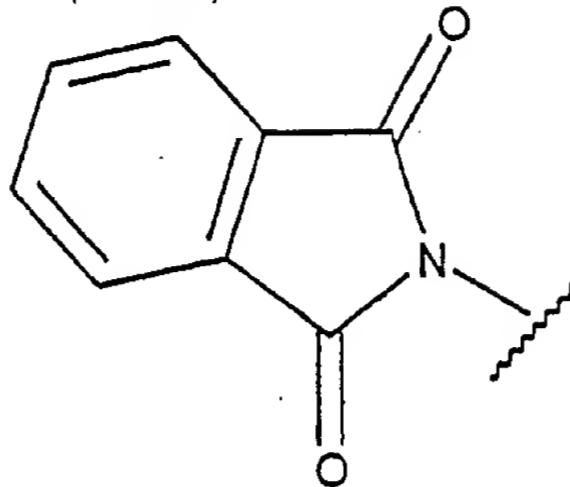
* alkyl (R), preferably $R = trityl, CH_3, CH_2CH_3, CH(CH_3)_2, C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea ($RNHCO$), preferably $R = CH_3, CH_2CH_3, CH(CH_3)_2, C(CH_3)_3$, phenyl, benzyl, allyl,

30

* phthalimide ($R^1=\emptyset$)



5

* biotin

* the group A can form with the nitrogen atom N with which it is contiguous an " NH_2^+ " entity

10

- Z_k , Z'_k and Z''_k can each represent independently:
hydrogen,

the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted by one or several of the following substituents:

1/ $-COOR_b$

2/ $-CONHR_b$

3/ $-COOH$

4/ $-OH$, OR_b

5/ $-NHR_b$

6/ $-NH_2$

7/ $-NH(CO)R_b$

25 8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

30 12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 atoms

a halogen

$-OR_b$

-COOR_b

-CONHR_b

-CONH₂

-CH₂COOR_b

5 -CH₂CONHR_b

-CH₂CONH₂

R_b representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

10

- -Ψ_k[*]- are independently either CO-NH peptide linkages, or linkages of different chemical natures selected particularly from the following list:

15 Ψ_k[*]- = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ; -N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ; -CH(F_k)=CH(F_{k'})- ; -CH₂NH- ; -NHCO- ; -NHCONH- ; -N(F_k)CON(F_{k'})- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ; -CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_{k'})- ; -CH₂-CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_{k'})CONH-

20 F_k and F_{k'} representing, independently of each other, hydrogen, the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

25

2/ an amino acid residue or an amino acid chain:

A-N(Z₁)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-

30

- "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,
- "k" is a whole number varying from 1 to m,
- A defined as above,

3/ a GP group which can be:

- a protective group selected from:

* oxycarbonyl ($GP = ROCO$), preferably Boc ($R =$

$C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxy-

carbonyl ($R = CH_2Ph$), allyloxycarbonyl ($R = -CH_2CH=CH_2$),

* acyl ($GP = RCO$), preferably $R = CH_3, CH_2CH_3, CH(CH_3)_2,$

$C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (R), preferably $R = trityl, CH_3, CH_2CH_3,$

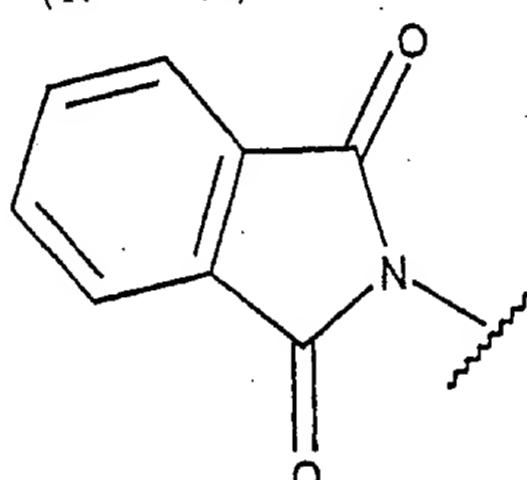
$CH(CH_3)_2, C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea ($RNHCO$), preferably $R = CH_3, CH_2CH_3, CH(CH_3)_2,$

$C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide ($R^1 = \emptyset$)



* biotin

* O_2 (corresponds to a nitro group as a masked amino form), $R^1 = \emptyset$

- the GP group which can also be such that the "GP-N" entity forms an " NH_2^+ " entity

- the groups R^1 , R^i and R can each represent independently of each other:

hydrogen,

halogen,

the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_a$

2/ $-CONHR_a$

3/ $-COOH$

- 4/ -OH
 5/ -OR_a
 6/ -NHR_a
 7/ -NH₂
 5 8/ -NH(CO)R_a
 9/ aryl, whose cyclic structure contains 5 to 20
 carbon atoms
 10 10/ halogen
 11/ carbonyl
 10 12/ nitrile
 13/ guanidine
 14/ nitro
 15 an aryl group, whose cyclic structure contains 5 to 20
 carbon atoms
 15 an OR_a group
 an NH₂ group
 an OH group
 -COOR_a
 -CONHR_a
 20 -CONH₂
 -CH₂COOR_a
 -CH₂CONHR
 -CH₂CONH₂
 25 R_a representing an allyl, benzyl, t-butyl,
 fluorenylmethyl, alkyl having 1 to 20 carbon atoms group,
 or an aryl group whose cyclic structure contains 5 to 20
 carbon atoms,
 30 - the B group can be either N-W' or O,
 - the W and W' groups can be or contain:
 A/ hydrogen,

B/ a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

- 1/ -COOR_h
- 5 2/ -CONHR_h
- 3/ -COOH
- 4/ -OH
- 5/ -OR_h
- 10 6/ -NHR
- 7/ -NH₂
- 8/ -NH(CO)R_h
- 9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

- 10/ halogen
- 15 11/ carbonyl of 1 to 10 carbon atoms
- 12/ nitrile
- 13/ guanidine

R_h representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

C/ an aryl group, whose cyclic structure contains 5 to 20 carbon atoms,

D/ a protected or unprotected side chain of amino acids selected from proteinogenic and non-proteinogenic acids and in the case of proline, W=W'=CH₂-CH₂-CH₂-CH(COOR)-)

E/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

- 30 -C(S'₁)(S''₁)-Ψ₁[*]-...-Ψ_{k-1}[*]-C(S'_k)(S''_k)-Ψ_k[*]-...Ψ_{h-1}[*]C(S'_h)(S''_h)-D
- "h" is a whole number greater than or equal to 1 and preferably 1 to 50, preferably 1 to 10,
- "k" is a whole number varying from 1 to h,
- D can be:

hydrogen,

-COOH

-COOR_c

-CONH₂

5 -CH₂COOR_c

-NHCOR_c

-NH (R_c)

-CONR_cR_d

-N (R_c) CON (R_d)

10 -OH

-OR_c

-CN

-C (O) R_c

15 R_c and R_d representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

20 - S_k, S'_k, and S''_k can each represent independently of each other:

hydrogen,

the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

25 a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

1/ -COOR_e

2/ -CONHR_e

3/ -COOH

30 4/ -OH

5/ -NHR_e

6/ -NH₂

7/ -NH (CO) R_e

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

5 11/ nitrile

12/ guanidine.

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

10 an NH₂ group

an OH group

a halogen

R_e representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- -Ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

Ψ_k[*]- = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ; -N(F_k)- ; -CON(F_k)- ; -CH₂CH₂ ; -CH(F_k)=CH(F_{k'})- ; -CH₂NH- ; -NHCO- ; -NHCONH- ; -N(F_k)CON(F_{k'})- ; -COCH₂- ; -CH(OH)CH₂- ; -CH(OH)CH₂NH- ; -CH₂O- ; -CH₂-NHCONH- ; CH(F_k)NHCON(F_{k'})- ; -CH₂-CONH- ; CH(F_k)CONH- ; -CH(F_k)CH(F_{k'})CONH-

25 F_k and F_{k'} representing, independently of each other, hydrogen, the protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, a halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

30 F/ an amino acid residue or a chain of amino acid residues:

-C(S'₁)(S''₁)-CO-N(S₂)-...-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-...CO-N(S_v)-C(S'_v)(S''_v)-D

- "v" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10 and preferably v>3 and v>5,

- "k" is a whole number varying from 1 to v,

5 - D, S_k, S'_k and S''_k are defined independently of each other as above,

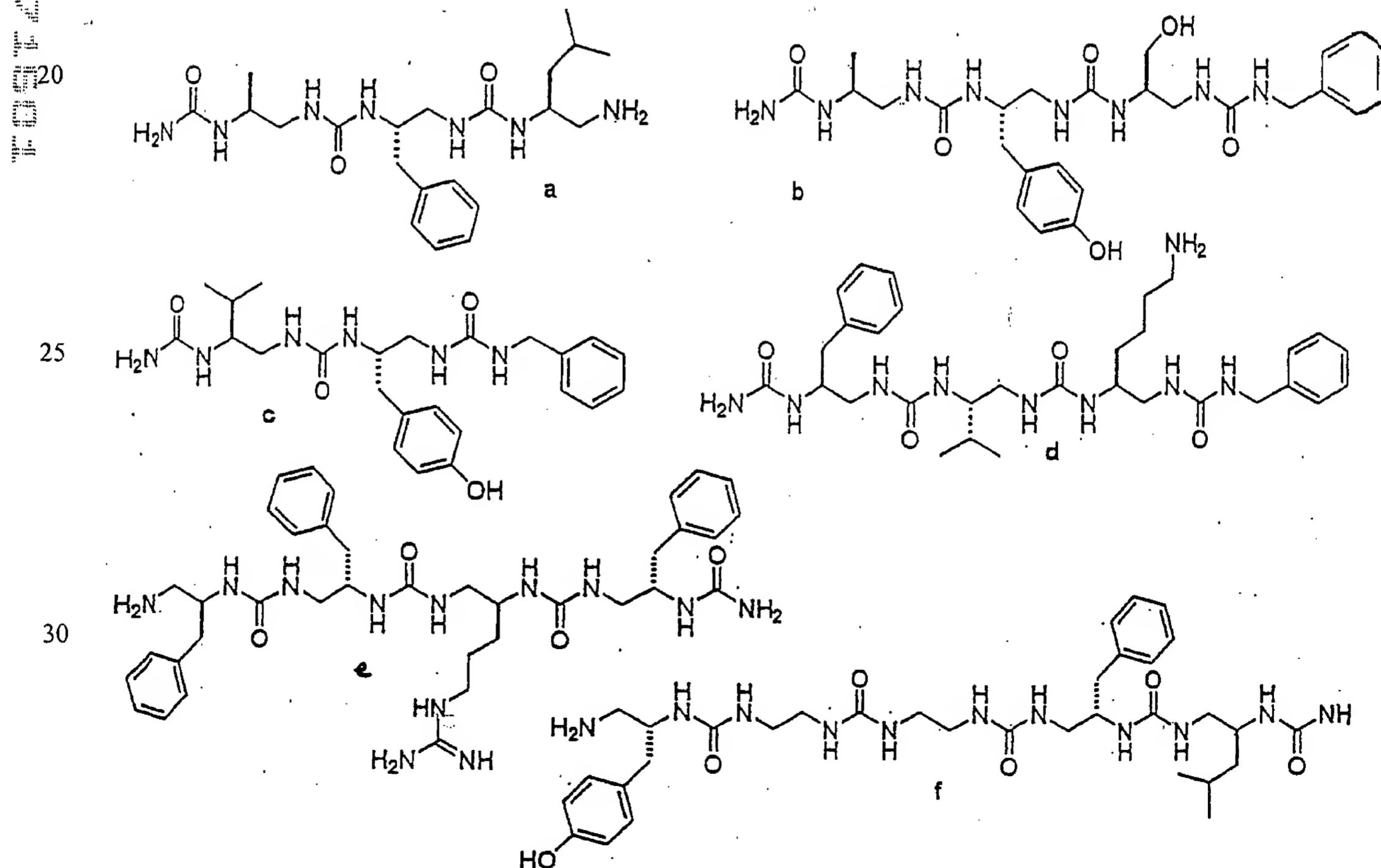
the compounds of formula (VII) moreover have the following property:

10 - if one or several asymmetric carbons are present in the formula (VII), then their configuration can be independently of each other either D (dextro) or L (levo),

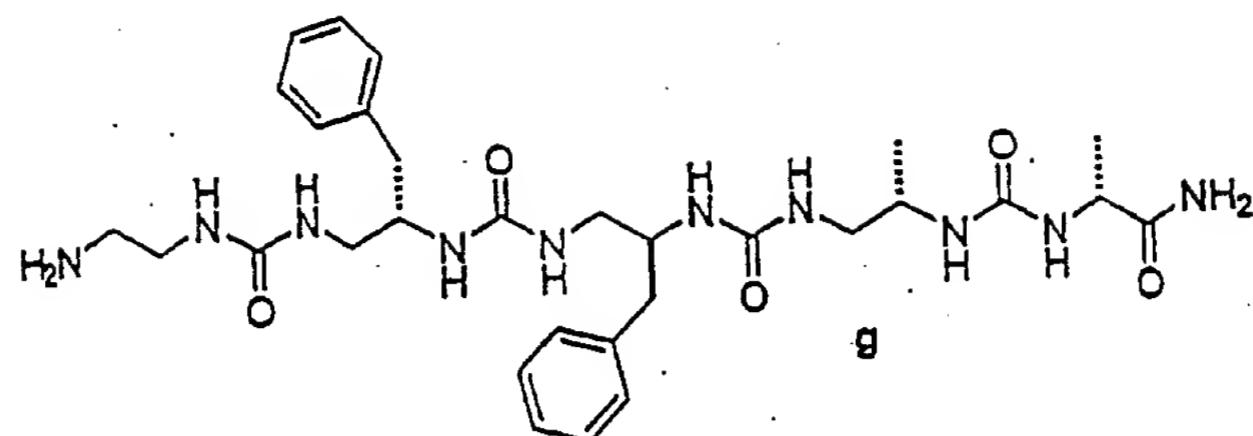
- the groups R¹ and Rⁱ can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between Rⁱ and R^{i+kc} (where kc is a positive whole number, preferably comprised from 1 to 3)

2/ cyclization between R¹ and Rⁱ wherein preferably i = 2, 3 or 4,



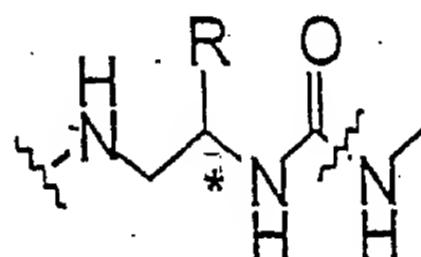
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10

provided that the compound of formula (VII) is different from the analogs of the peptide Tyr-Gly-Gly-Phe-Leu-OH, containing one or several derivatives as defined below mimicking the side chain of the amino acids present in the peptide and permitting the introduction of one or several urea linkages, which is to say the compound of formula (VII) is different from the following compounds:

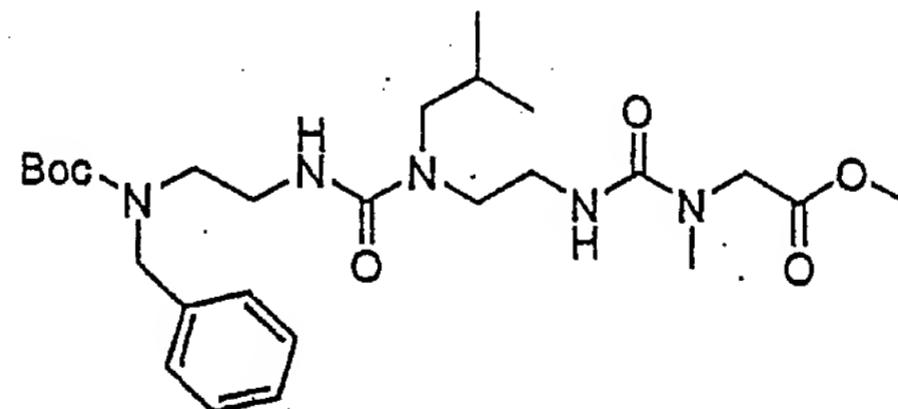
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in which R represents hydroxybenzyl, a hydrogen atom, a benzyl group, or an isobutyl group.

provided that the compound of formula (VII) is different from:



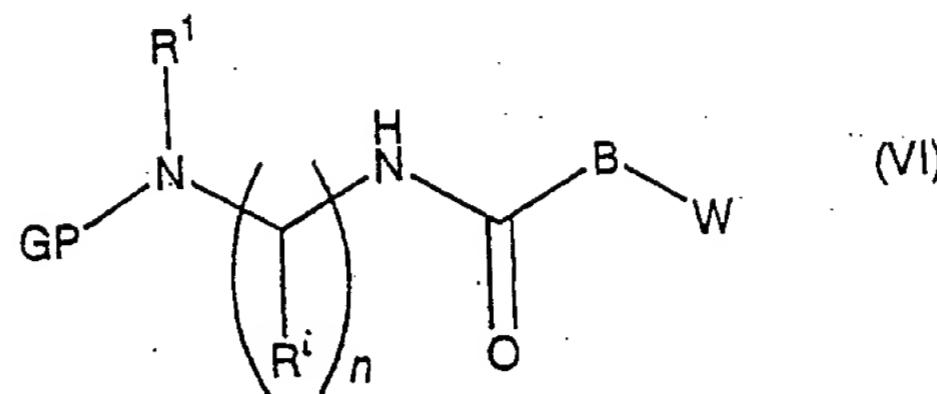
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In formula (VII), when B represents N-W', N corresponds to the nitrogen atom, and when B represents O, O corresponds to the oxygen atom.

The compounds of type (VII) are reaction products of compounds of type (III) and (III bis) or possibly (IV) with derivatives containing a primary or secondary amine or an alcohol.

The invention also relates to compounds of formula (VI)

5



10

in which n , i , GP , R^1 , R^i , B and W have the meanings mentioned above with respect to formula (VII).

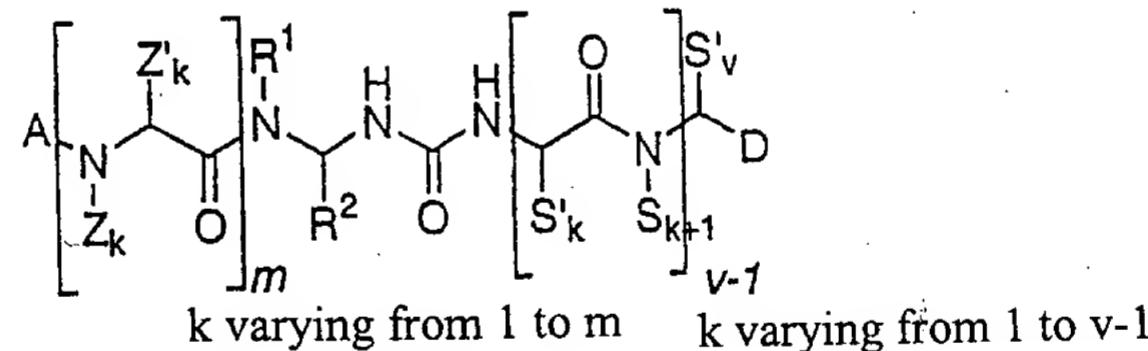
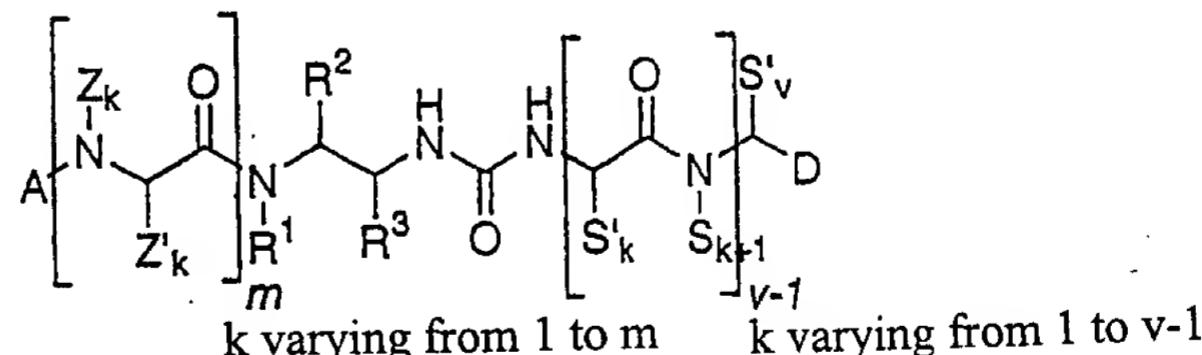
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Compounds of type (VI) are reaction products of the compounds of type (I) and (I bis) or possibly (II) with derivatives containing a primary or secondary amine or an alcohol.

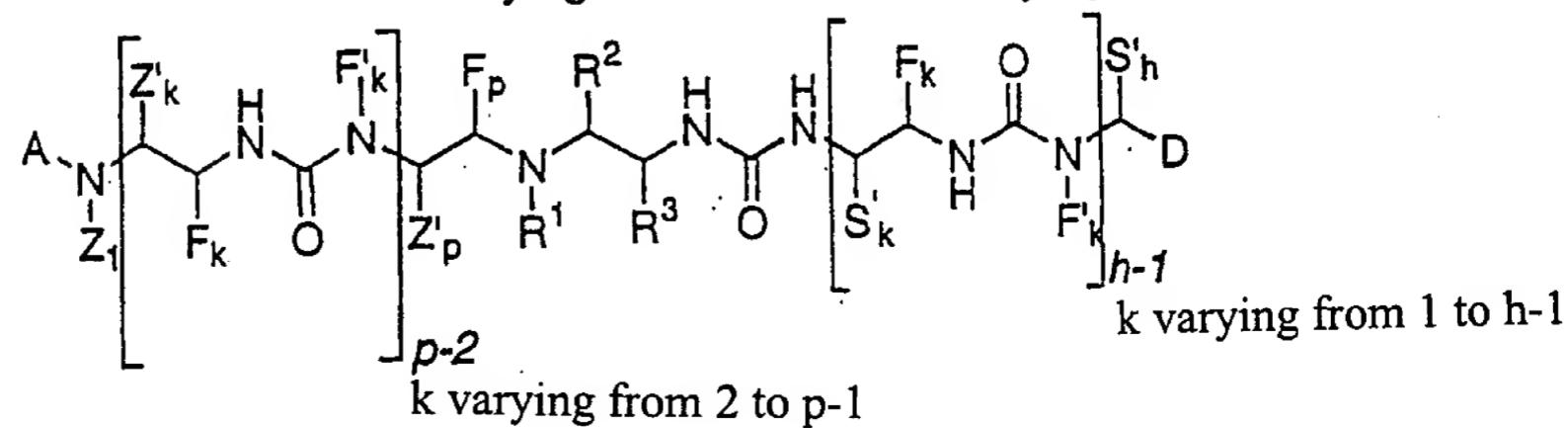
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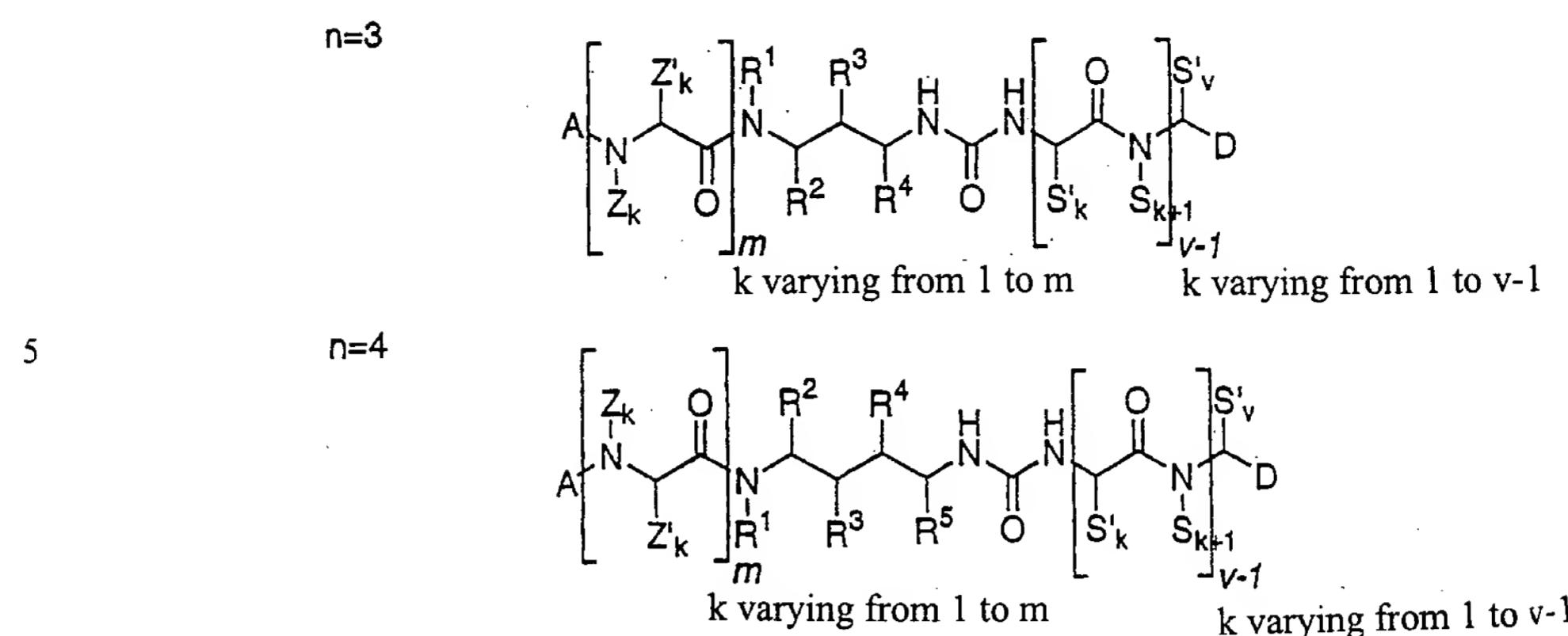
A preferred group of compounds of formula (VII) is constituted by those in which $1 \leq n \leq 4$, and particularly the following compounds in which v , h , m and p are comprised from 1 to 10 and preferably 1 to 5 and more particularly the following compounds:

25

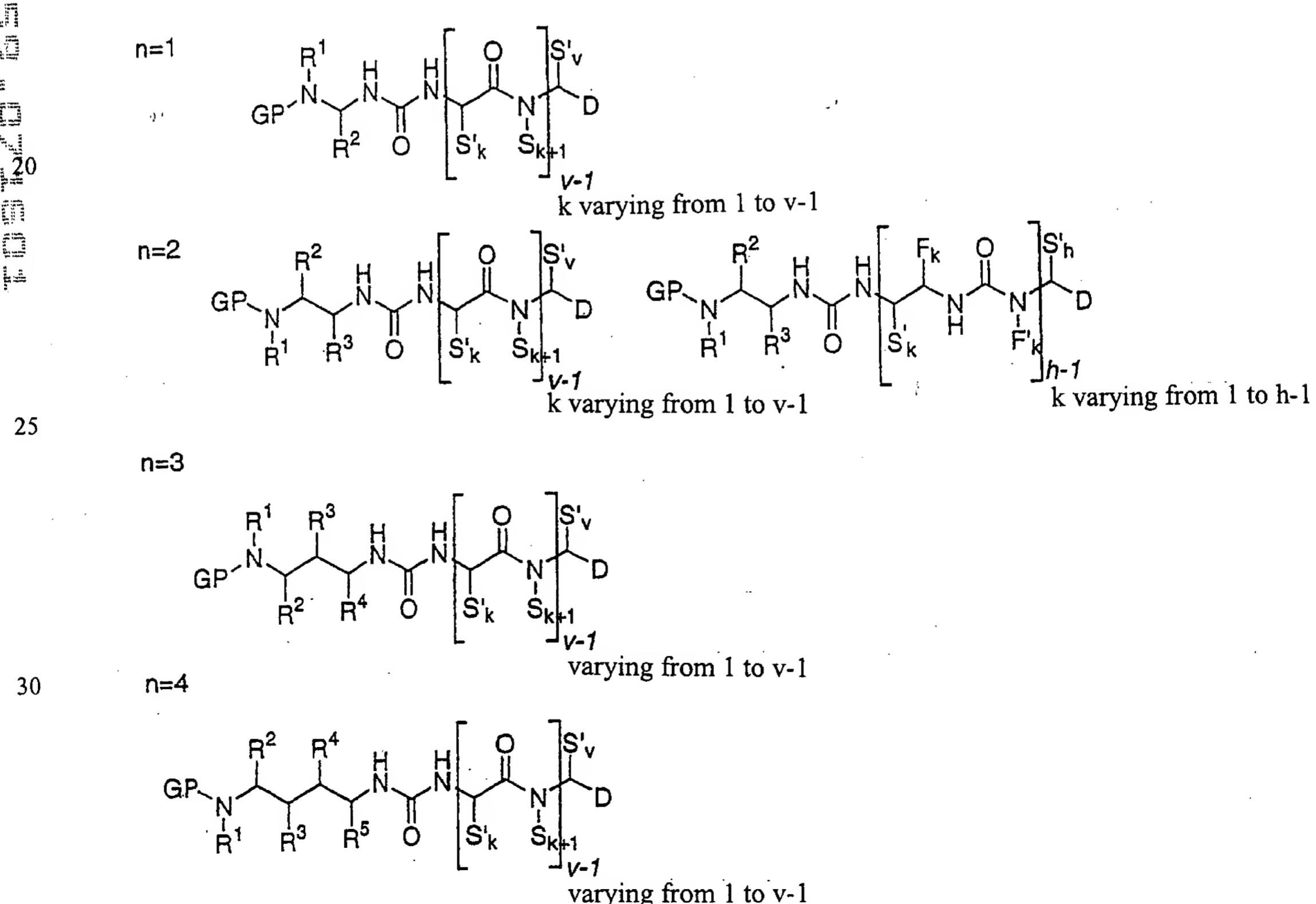
 $n=1$  k varying from 1 to m k varying from 1 to $v-1$ $n=2$  k varying from 1 to m k varying from 1 to $v-1$

30

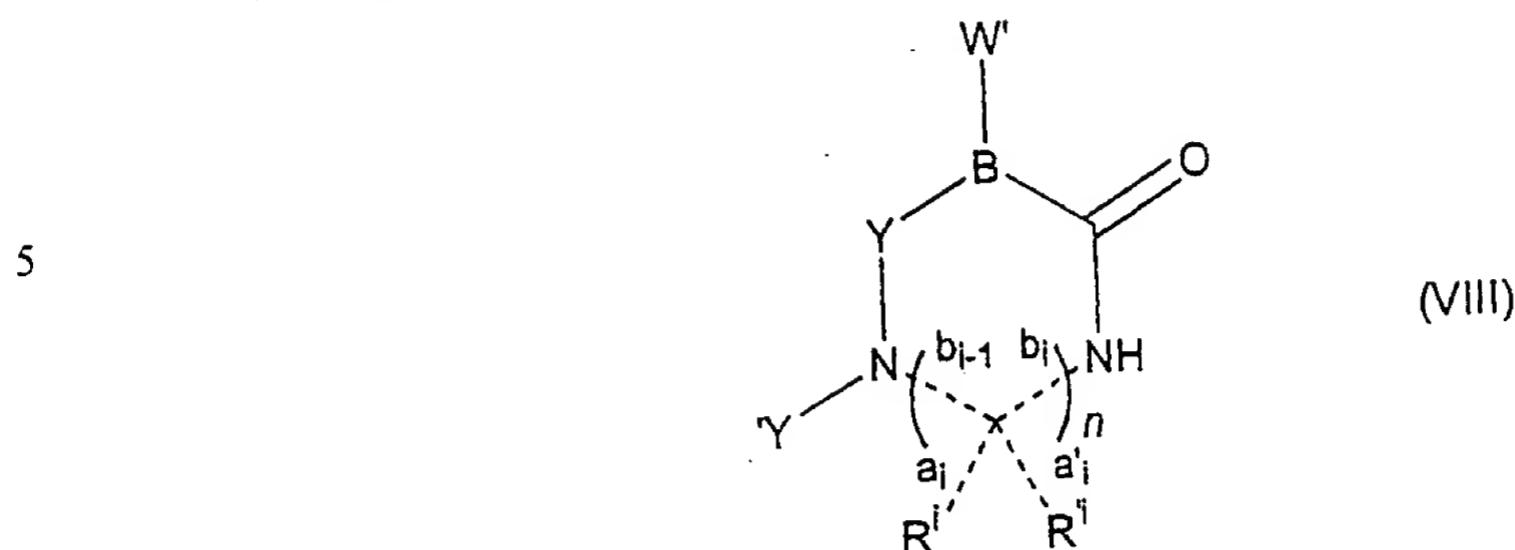
 k varying from 2 to $p-1$ k varying from 1 to $h-1$



A preferred group of compounds is constituted by those of formula (VI) in which $1 \leq n \leq 4$, GP is an oxycarbonyl or acyl group as defined above with respect to the compounds of formula (VI), and more particularly the following compounds in which *v* and *h* are comprised between 1 and 10, and preferably equal to 1 or 2, and particularly those in which GP = Boc and Fmoc:



The invention also relates to compounds of the formula (VIII)



10

in which:

the total number of atoms forming the cycle is greater than seven,

the groups R^i , R'^i , Y' , W' , B have the meanings already indicated above,

the group Y in this new case can be or contain:

I/ a (C1-C20) alkyl group, unsubstituted or substituted with one or more substituents from the following:

- 1/ -COOR_e
2/ -CONHR_e
3/ -COOH
4/ -OH
25
5/ -OR
6/ -NHR_e
7/ -NH₂
8/ -NH(CO)R_e
9/ aryl, whose cyclic structure contains 5 to 20
30 carbon atoms,
10/ halogen
11/ carbonyl of 1 to 10 carbon atoms
12/ nitrile
13/ guanidine

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

II/ an aryl group

5 III/ a pseudopeptide (peptide containing one or several pseudopeptidic linkages)

(on $B \leftarrow -C(Z'_1)(Z''_1)-\psi_1[*]-\dots-\psi_{k-1}[*](Z_k)-C(Z'_k)(Z''_k)-\psi_k[*]-\dots-\psi_{p-1}[*]C(Z'_p)(Z''_p)-CO-(\rightarrow on NY')$)

10 - "p" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- Z_k , Z'_k and Z''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic or non-proteinogenic amino acids

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_b$

2/ $-CONHR_b$

3/ $-COOH$

4/ $-OH$, OR_b

5/ $-NHR_b$

6/ $-NH_2$

25 7/ $-NH(CO)R_b$

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

30 11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

- COOR_b
- CONHR_b
- CONH₂
- CH₂COOR_b
- 5 -CH₂CONHR_b
- CH₂CONH₂

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

10 - -ψ_k[*]- are independently either CO-NH peptidic linkages or linkages of different chemical natures selected particularly from the following list:

- ψ_k[*]- = -CH₂CH₂; -CH(F_k)=CH(F_k')-; -CH₂NH-; -NHCO-; -NHCONH-;
- COCH₂-; -CH(OH)CH₂-; -CH(OH)CH₂NH-; -CH₂-; -CH(F_k)-; -CH₂O-;
- CH₂-NHCONH-; CH(F_k)NHCONF_k'-; CH₂-CONH-; CH(F_k)CONH-;
- CH(F_k)CH(F'_k)CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

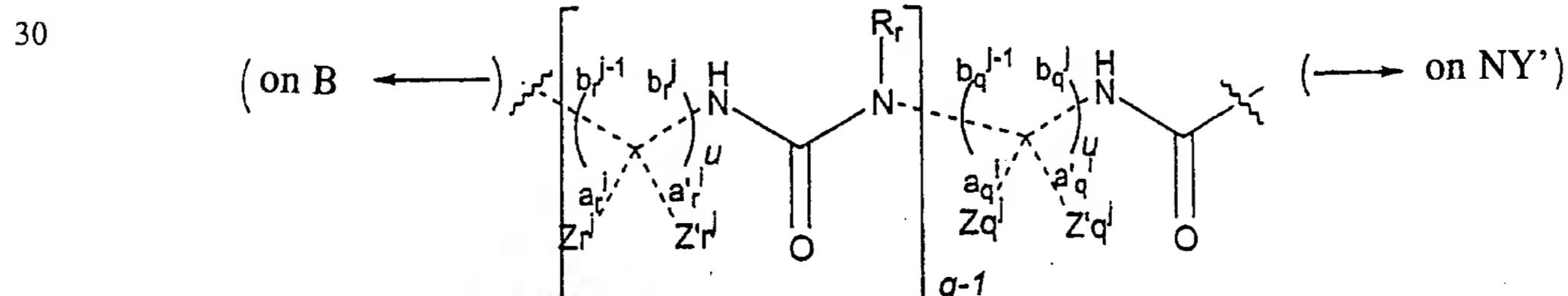
IV/ an amino acid residue or a chain of amino acid residues:

(on B←)-C(Z'₁)(Z''₁)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-(→ on NY')

25 - "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- Z_k, Z'_k, and Z''_k are defined as before.

V/ an oligomer of urea defined as follows:



- "u" is a whole number greater than or equal to 1, preferably 1 to 50, and preferably 1 to 10,

- "q" is a whole number greater than or equal to 1, preferably 1 to 50; and preferably 1 to 10,

5 - "j" is a whole parameter comprised between 2 and u+1,

- "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q-1.

- " a_r^j " and " a'_r^{j+1} ", represented by a broken line, are covalent bonds which can be single (s), or double (d),

10 "b_r^j" and " b_r^{j-1} ", shown by broken line, are covalent bonds which can be simple (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s),

* if $b_r^j = d$, then a_r^j and $a_r^{j+1} = s$; a'_r^j and $a'_r^{j+1} = \emptyset$;

b_r^{j-1} and $b_r^{j+1} = s$

* if $b_r^j = t$, then a_r^j and $a_r^{j+1} = \emptyset$; a'_r^j and $a'_r^{j+1} = \emptyset$;

b_r^{j-1} and $b_r^{j+1} = s$

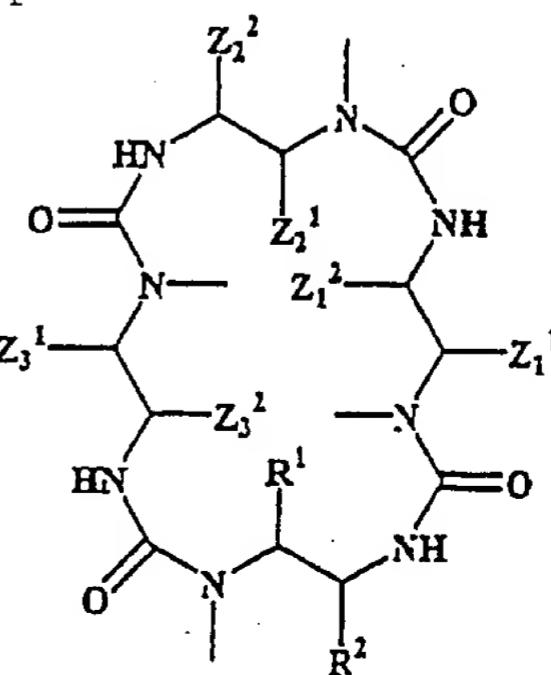
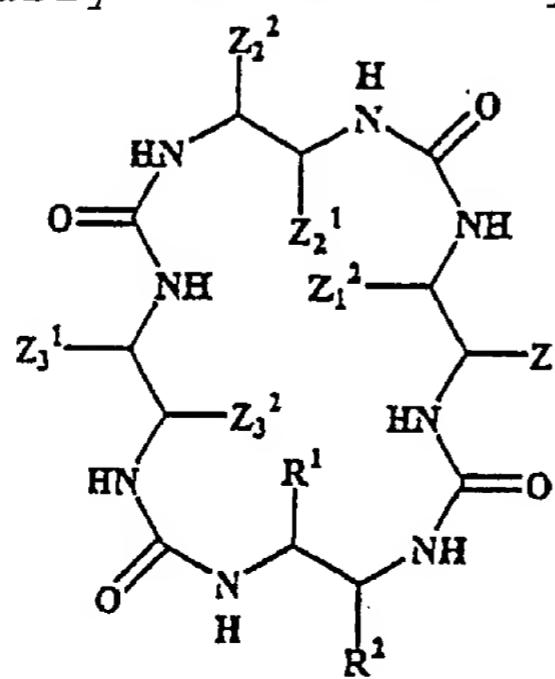
* if $a_r^j = d$, then b_r^{j-1} and $b_r^j = s$,

certain of these bonds can also form a part of aromatic rings,

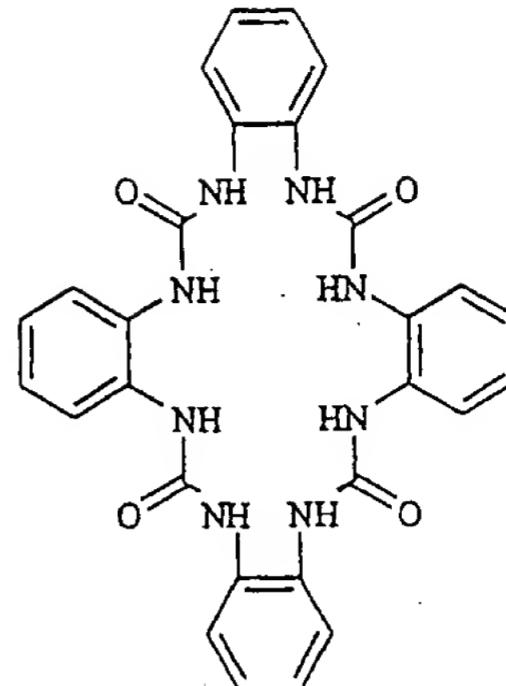
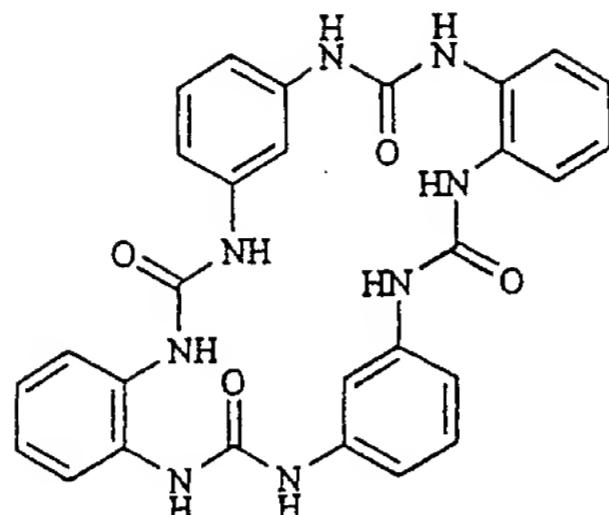
Z_r , Z_r^j , Z'_r^j have meanings indicated with respect to R^1 , R^i , R'^i as defined above.

A preferred group of compounds of formula (VIII) is constituted by those in which $1 \leq n \leq 4$, and particularly the following compounds in which h, v, t, p, m, and q are comprised from 1 to 10 and preferably 1 to 5, and more particularly the following compounds:

30



5

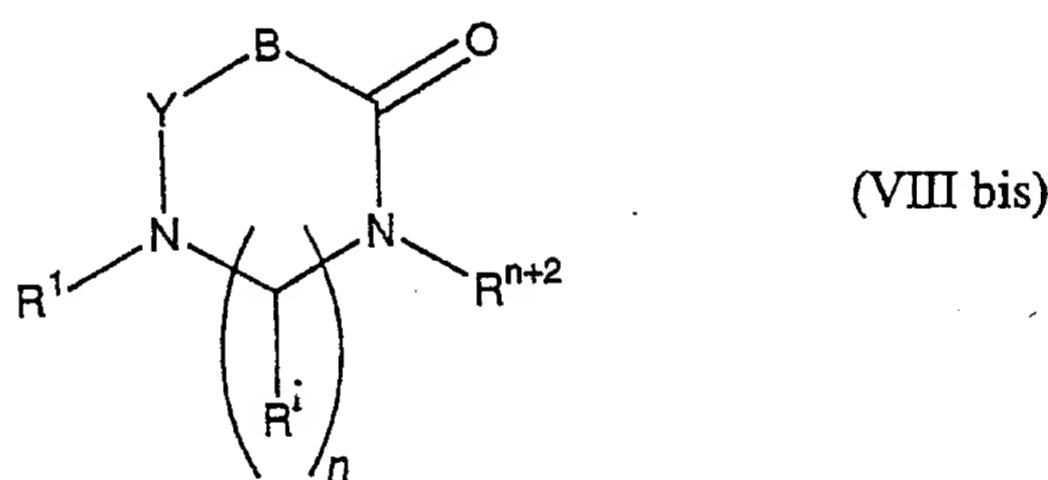


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in which R^1 and R^2 have the meanings indicated above and in which Z_1^1 , Z_1^2 , Z_2^1 , Z_2^2 , Z_3^1 and Z_3^2 have the meanings indicated with respect to Z_r^j .

The invention also has for its object cyclic compounds of formula (VIII bis)

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in which:

the total number of atoms forming the cycle is greater than six, preferably greater than or equal to 7,

- 25 - "n" is a whole number greater than or equal to 1, preferably from 1 to 10, preferably from 1 to 4,
 - "i" is a whole number varying from 2 to $n+1$,
 - the groups R^1 , R^i and R^{n+2} each can represent independently of each other:

30 hydrogen

halogen

the protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents of the following:

- 1/ -COOR_a
- 2/ -CONHR_a
- 5 3/ -COOH
- 4/ -OH
- 5/ -OR_a
- 6/ -NHR_a
- 7/ -NH₂
- 10 8/ -NH(CO)R_a
- 9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms
- 10/ halogen
- 11/ carbonyl of 1 to 10 carbon atoms
- 12/ nitrile
- 13/ guanidine
- 14/ nitro
- an aryl group, whose cyclic structure contains 5 to 20 carbon atoms
- an OR_a group
- an NH₂ group
- an OH group
- COOR_a
- CONHR_a
- 25 -CONH₂
- CH₂COOR_a
- CH₂CONHR_a
- CH₂CONH₂
- R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,
- 30 the groups R¹ and Rⁱ can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R^{i+kc} (where kc is a positive integer, preferably between 1 and 3)

2/ cyclization between R^i and R^i wherein preferably $i = 2, 3$ or 4 ,

5 - the Y group can be or contain:

I/ a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ $-CONHR_e$

10 3/ $-COOH$

4/ $-OH$

5/ $-OR$

6/ $-NHR_e$

7/ $-NH_2$

8/ $-NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms,

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_e representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

25 II/ an aryl group

III/ a pseudopeptide (peptide containing one or several pseudopeptidic bonds)

(sur B \leftarrow) -C(Z'₁)(Z''₁)- $\Psi_1[*]$ -...- $\Psi_{k-1}[*]$ -C(Z'_k)(Z''_k)- $\Psi_k[*]$ -...- $\Psi_{p-1}[*]$ C(Z'_p)(Z''_p)- $\Psi_p[*]$ -(\rightarrow sur NR¹)

30

- "p" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- Z_k, Z'_k and Z''_k can each represent independently of each other:

35 hydrogen,

the protected or unprotected side chain of an amino acid selected from proteinogenic or non-proteinogenic amino acids,

5 a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

- 1/ -COOR_b
- 2/ -CONHR_b
- 3/ -COOH
- 4/ -OH, OR_b
- 10 5/ -NHR_b
- 6/ -NH₂
- 7/ -NH(CO)R_b

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-COOR_b

-CONHR_b

-CONH₂

25 -CH₂COOR_b

-CH₂CONHR_b

-CH₂CONH₂

R_b representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

30 - -Ψ_k[*] - are independently either CO-NH peptidic linkages or linkages of different chemical natures selected particularly from the following list:

$\psi_k^*[-] = -\text{CH}(F_k)- ; -\text{CO}- ; -\text{N}(F_k)\text{CO}- ; -\text{CH}(F_k)\text{CO}- ; -\text{CH}(F_k)\text{NHCO}- ; -\text{N}(F_k)- ;$
 $-CON(F_k)- ; -\text{CH}_2\text{CH}_2 ; -\text{CH}(F_k)=\text{CH}(F_k')- ; -\text{CH}_2\text{NH}- ; -\text{NHCO}- ; -\text{NHCONH}- ;$
 $-N(F_k)\text{CON}(F_k')- ; -\text{COCH}_2- ; -\text{CH}(\text{OH})\text{CH}_2- ; -\text{CH}(\text{OH})\text{CH}_2\text{NH}- ; -\text{CH}_2\text{O}- ;$
 $-CH_2\text{-NHCONH}- ; \text{CH}(F_k)\text{NHCON}(F_k')- ; -\text{CH}_2\text{-CONH}- ; \text{CH}(F_k)\text{CONH}- ;$
 $-\text{CH}(F_k)\text{CH}(F_k')\text{CONH}-$

5

10

F_k and F_k' representing, independently of each other, hydrogen, a protected or unprotected side chain of an amino acid selected from proteinogenic and proteinogenic amino acids, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

IV/ an amino acid residue or a chain of amino acid residues:

(sur B \leftarrow)-C(Z'1)(Z''1)-CO-N(Z₂)-...-CO-N(Z_k)-C(Z'k)(Z''k)-CO-N(Z_{k+1})-...CO-N(Z_m)-C(Z'm)(Z''m)-CO-(\rightarrow sur NR¹)

15

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- "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- Z_k , $Z'k$, and $Z''k$ are defined as above,

- the B group can be either N-W' or O,

- the W' group can be or contain:

A/ hydrogen,

B/ a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -COOR_h

2/ -CONHR_h

3/ -COOH

4/ -OH

5/ -OR_h

6/ -NHR

7/ -NH₂

8/ -NH(CO)R_h

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms,

10/ halogen

5 11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_h representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

C/ an aryl group, whose cyclic structure contains 5 to 20 carbon atoms,

D/ a protected or unprotected amino acid side chain selected from proteinogenic and non-proteinogenic amino acids and in the case of prolin, W = W' = -CH₂-CH₂-CH₂-CH(COOR)-)

E/ a pseudopeptide (peptide containing one or several pseudopeptidic linkages).

-C(S'₁)(S''₁)-Ψ₁[*]-...-Ψ_{k-1}[*]-C(S'_k)(S''_k)-Ψ_k[*]-...Ψ_{h-1}[*]C(S'_h)(S''_h)-D

- "h" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

- "k" is a whole number varying from 1 to h,

25 - D can be:

hydrogen,

-COOH

-COOR_c

-CONH₂

30 -CH₂COOR_c

-NHCOR_c

-CONR_cR_d

-N(R_c)CON(R_d)

-OH

DEPOULEE PAR LE 20 SEPTEMBRE 1985

-OR_c

-CN

-C(O)R_c

R_c and R_d representing an allyl, benzyl, t-butyl,
5 fluorenylmethyl, alkyl having 1 to 20 carbon atoms group,
or an aryl group whose cyclic structure contains 5 to 20
carbon atoms,

10 - S_k, S'_k and S''_k can each represent independently of
each other:

hydrogen,

the protected or unprotected side chain of an amino
acid selected from proteinogenic and non-proteinogenic
amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted
with one or several substituents from the following:

1/ -COOR_e

2/ -CONHR_e

3/ -COOH

4/ -OH

5/ -NHR_e

6/ -NH₂

7/ -NH(CO)R_e

25 8/ aryl, whose cyclic structure contains 5 to 20
carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

30 an aryl group, whose cyclic structure contains 5 to 20
carbon atoms

an OR_e group

an NH₂ group

an OH group

halogen

R_e representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- $\Psi_k^*[-]$ are independently either CO-NH peptidic linkages or linkages of different chemical nature selected particularly from the following list:

$\Psi_k^*[-] = -CH(F_k)- ; -CO- ; -N(F_k)CO- ; -CH(F_k)CO- ; -CH(F_k)NHCO- ; -N(F_k)- ;$
 $-CON(F_k)- ; -CH_2CH_2 ; -CH(F_k)=CH(F_k')- ; -CH_2NH- ; -NHCO- ; -NHCONH- ;$
 $-N(F_k)CON(F_k')- ; -COCH_2- ; -CH(OH)CH_2- ; -CH(OH)CH_2NH- ; -CH_2O- ;$
 $-CH_2-NHCONH- ; CH(F_k)NHCON(F_k')- ; -CH_2-CONH- ; CH(F_k)CONH- ;$
 $-CH(F_k)CH(F_k')CONH-$

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F_k and F_k' representing, independently of each other, hydrogen, a protected or unprotected side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

F/ an amino acid residue or chain of amino acid residues:

$-C(S'_1)(S''_1)-CO-N(S_2)-...-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-...CO-N(S_v)-$
 $C(S'_v)(S''_v)-D$

25

- "v" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10 with preferably $v>3$ and $v>5$,

- "k" is a whole number varying from 1 to v,

30 - D, S_k , S'_k and S''_k are defined independently as above,

and more particularly the compounds responding to the formula (VIII bis) in which $1 \leq n \leq 4$, h, v, p and m are comprised from 1 to 10 and preferably 1 to 5.

The compounds of the (VIII) and (VIII bis) type are cyclic compounds obtained from compounds of the (III) and (III bis) or (IV) type and by intramolecular reaction with an amine liberated after elimination of temporary protection.

The compounds of type (VIII) and (VIII bis) are cyclic compounds obtained from compounds of type (III) and (III bis) or (IV) and by intramolecular reaction with an amine freed after elimination of temporary protection.

In the compounds of formula (I), (I bis), (III), (IIIBis), (IV), (V), (Vbis), (VI) and (VII), the aryl group is preferably selected from:

- 1/ phenyl
- 2/ naphthyl
- 3/ indenyl
- 4/ thiophenyl
- 5/ benzothiophenyl
- 6/ furanyl
- 7/ benzofuranyl
- 8/ pyridyl
- 9/ indolyl
- 10/ pyrrolyl

or the aryl group can be substituted with 1 to 6 substituents selected particularly from:

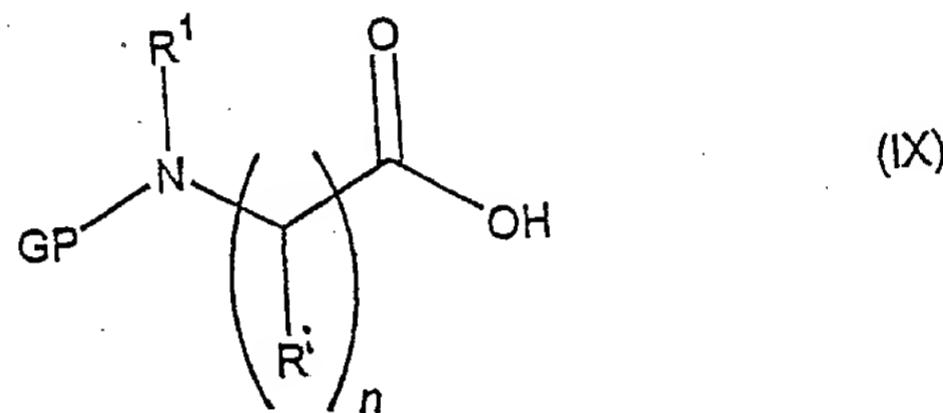
- 1/ alkyl of 1 to 10 carbon atoms
- 2/ halogen
- 3/ alkoxy of 1 to 10 carbon atoms
- 4/ hydroxyl
- 5/ amine of 1 to 10 carbon atoms
- 6/ ester of 1 to 10 carbon atoms
- 7/ nitrile
- 8/ aryl, whose cycle structure contains 5 to 20 carbon atoms
- 9/ nitro

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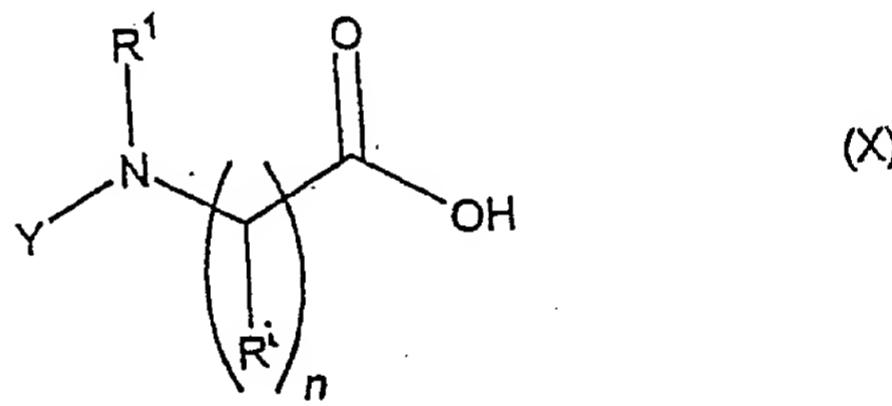
- 10/ urea of 1 to 10 carbon atoms
 11/ amide of 1 to 10 carbon atoms
 12/ guanidine
 13/ carboxylic acid of 1 to 10 carbon atoms.

5 According to a preferred embodiment of the process of the invention, the preparation of the compounds of formula (I bis), (II), (III bis), (IV), (V) or (Vbis) can be carried out from respectively:

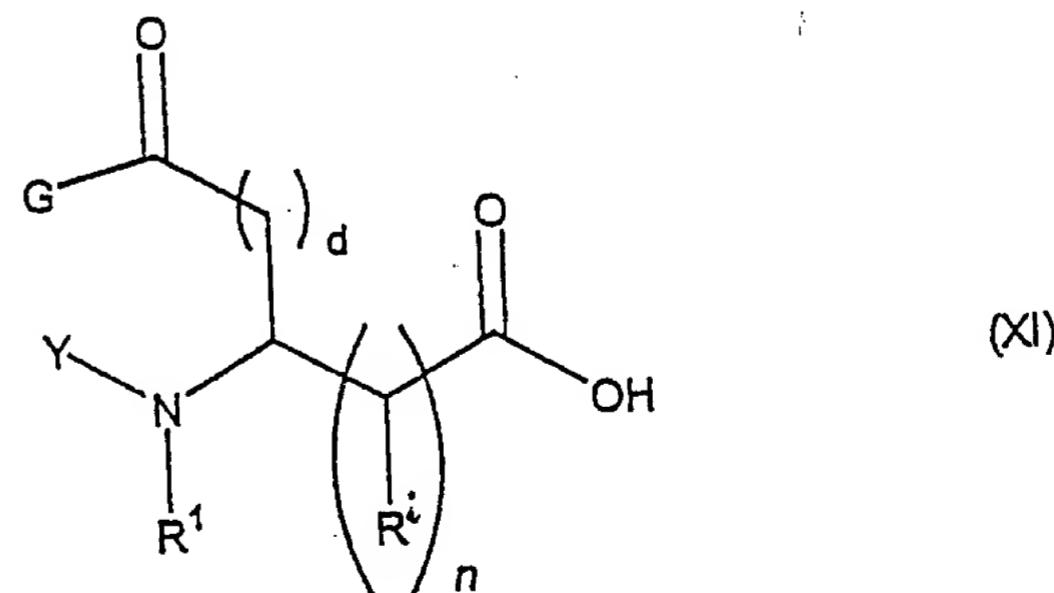
10 - compounds of formula (IX) (for compounds of formula (I bis) and (II))



15 - compounds of formula (X) (for compounds of formula (III bis) and (IV))



20 - compounds of formula (XI) (for compounds of formula (V) and (Vbis))

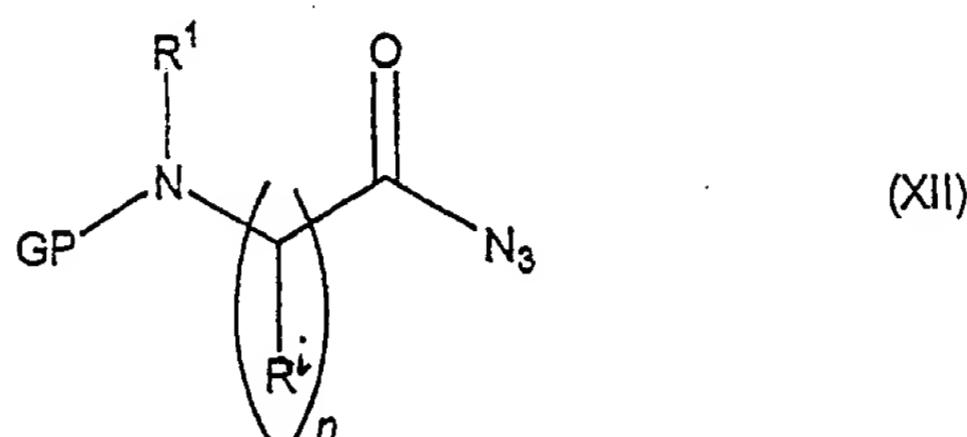


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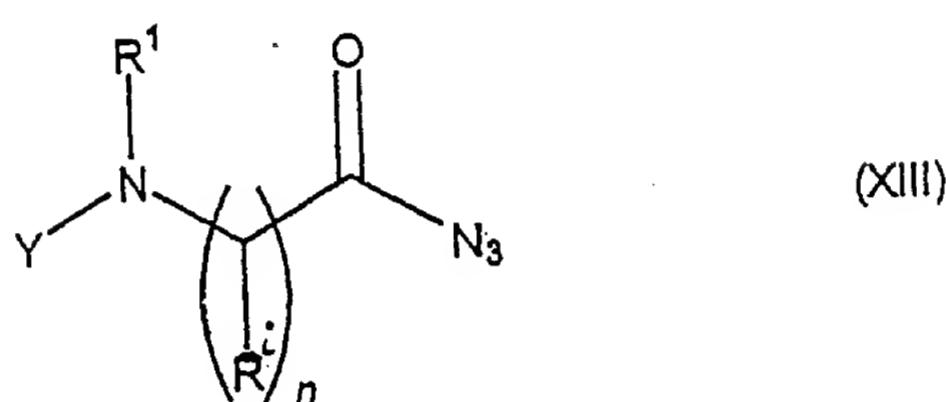
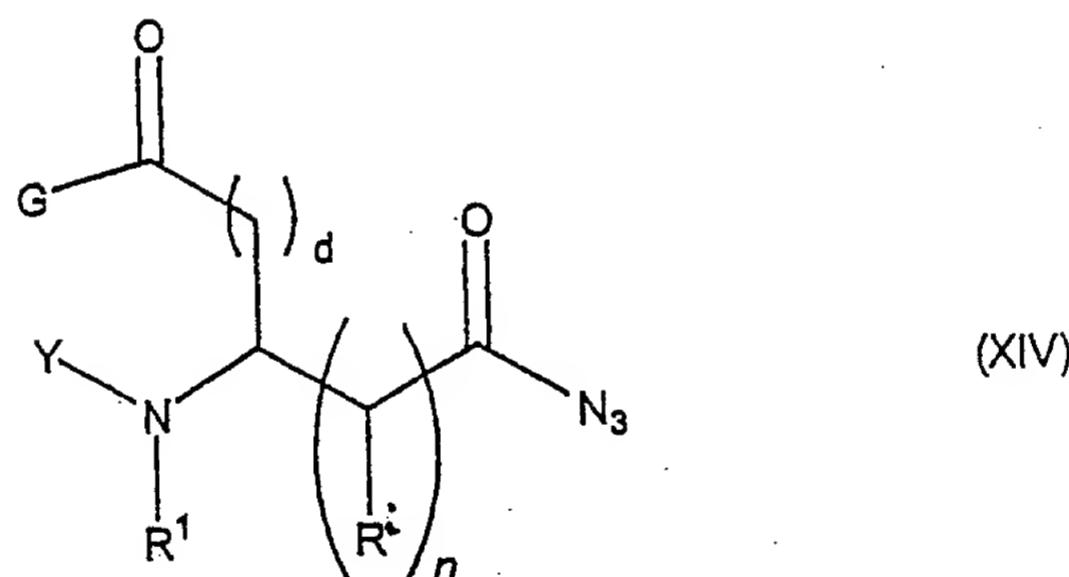
and comprises

(a) a step of transformation of the acid (IX) or (X) or (XI) into a corresponding acyl azide (XII) or (XIII) or (XIV) respectively,

5



10

15
20
25
30

25

by a suitable treatment,

(b) a step of transformation of the acyl azide (XII) or (XIII) or (XIV) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) or (Vbis), respectively,

(c) a step of treatment of the isocyanate (II), (IV) or (V bis), preferably not isolated, under conditions permitting obtaining a derivative of the carbamic acid of formula (I bis), (III bis) or (V).

According to a preferred embodiment of the process of preparation of the invention:

- step a) of transformation of the acid (IX) or (X) or (XI) into the corresponding acyl azide (XII) or (XIII) or (XIV) respectively, is carried out for example by treatment of the mixed anhydride (formed by reaction of acid (IX), (X) or (XI) with ethyl or isobutyl chloroformate in the presence of a tertiary amine such as NMM (N-methylmorpholine), DIEA (di-isopropylethylamine) or Et₃N in THF (tetrahydrofuran)) with a sodium azide solution,

- step b) of transformation of the acyl azide (XII) or (XIII) or (XIV) into the corresponding isocyanate (II) or (IV) or (Vbis), respectively, is carried out for example by heating a solution of the acyl azide in a suitable solvent, particularly toluene or xylene, the formation of the isocyanate being followed by observation of the release of gas into the balloon, the end of the gaseous emission signifying completion of the Curtius rearrangement,

- step c) of treatment of the corresponding isocyanate (II) or (IV) or (Vbis) is carried out, when the isocyanate is in solution, for example in hot toluene, with one of the derivatives from the following list:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

- imidazole
- tetrazole

(permitting obtaining a pre-activated synthon) and if desired a base such as pyridine, to obtain a carbamic acid derivative of formula (I bis), (III bis) or (V), which is then preferably isolated, preferably by crystallization or by purification, particularly on a silica column, or by HPLC or by aqueous, acid or basic washing after dissolution in an organic solvent.

By way of example, in step a) described above, the mixed anhydride is formed by reaction of the acid (IX), (X) or (XI) with ethyl or isobutyl chloroformate in the presence of a tertiary amine such as NMM (N-methylmorpholine), DIEA (di-isopropylethylamine) or Et₃N in THF (tetrahydrofuran) at a temperature of -15°C.

By way of example, in step b) described above, the solution of acyl azide is heated in a suitable solvent (particularly toluene or xylene), to a temperature of 65°C.

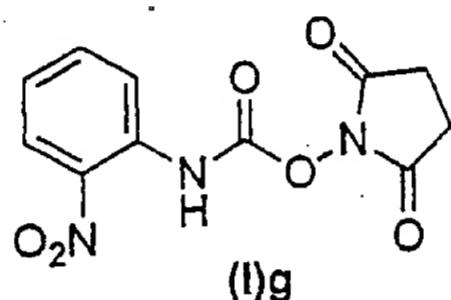
By way of example, in step c) described above, the treatment of the isocyanate is carried out, when it is in solution, for example in hot toluene, at a temperature of 65°C.

According to another embodiment of the invention, the process of preparation of the compounds of formula (VI) or (VII) comprises the reaction of compounds containing primary or secondary amines or alcohols, with one of the products of formula (I bis), (II), (III bis), (IV), (V) or (Vbis) defined above, for example in a solvent such as DMF, H₂O/acetone, THF, dichloromethane or acetonitrile with or without the addition of a base such as a tertiary amine (for example Et₃N, DIEA, NMM, collidine, lutidine) or such as sodium carbonate (Na₂CO₃) or sodium bicarbonate (NaHCO₃).

According to another preferred embodiment of the invention, the process of preparation of the compounds of

formula (VIII bis) comprises the intramolecular cyclization of products of formula (III bis) or compounds of formula (VII), for example in a solvent such as DMF, H₂O/acetone, THF, dichloromethane or acetonitrile with or without the addition of a base such as a tertiary amine (for example Et₃N, DIEA, NMM, collidine, lutidine) or such as sodium carbonate (Na₂CO₃).

Figure 1: Figure 1 corresponds to the X-ray structure of the carbamate (**Ig**) corresponding to the following formula:



The invention is illustrated hereafter by examples I to III, which have no limiting value.

In example I, the reaction of the O-succinimidyl-2-(tert-butoxycarbonylamino)-ethylcarbamate derivatives with aliphatic or aromatic primary amines, secondary amines, or α- or β-amino acid derivatives, rapidly gives urea derivatives or urea oligomers with a high yield.

In example II, the O-succinimidyl-2-[(9H-fluoren-9-ylmethoxy)carbonylamino]-ethylcarbamate derivatives used in a repetitive manner in solid phase permit obtaining the desired urea pseudopeptides and urea oligomers, with a high yield.

EXAMPLE I

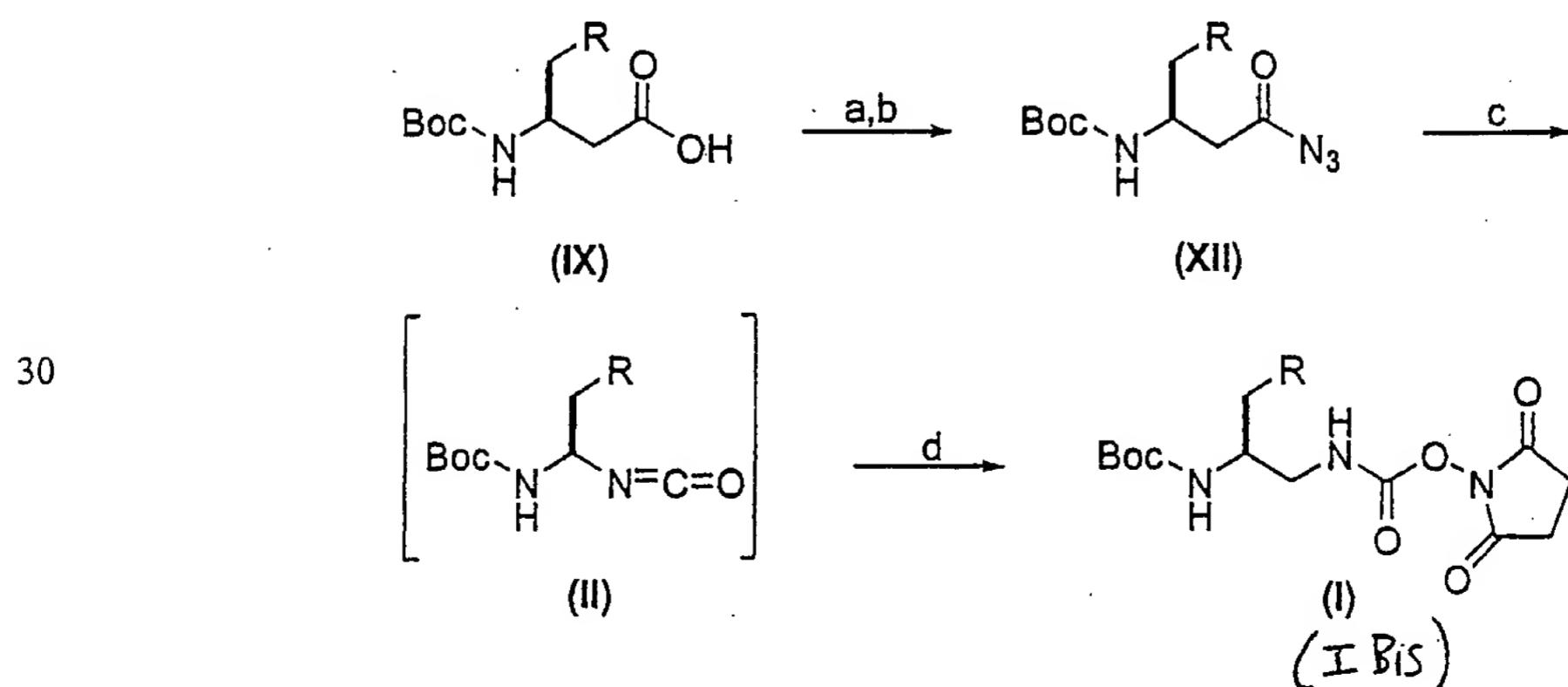
An efficacious synthesis of O-succinimidyl-2-(tert-Butoxycarbonylamino)-ethylcarbamate derivatives (**I**) and (**Ibis**) is described as well as their utilization as monomers active in the synthesis of di- and tri-substituted ureas and urea oligomers. The β-amino N-Boc-protected acids

(**IX**) are first transformed into the corresponding acyl azide derivatives (**XII**). The isocyanate formed by Curtius rearrangement of compounds (**XII**) is immediately treated with N-hydroxysuccinimide in the presence of pyridin to give the corresponding carbamates (**I**) and (**Ibis**) (see the formula of reaction 1) (50-64%). These carbamates are stable and crystalline compounds which react spontaneously with primary and secondary amines at ambient temperature to give (**VIE**) ureas (79-87%). By way of example, the synthesis of the N-boc-protected tri-urea derivative (**VIg**) has also been carried out by step-by-step addition using carbamate (**Ib**).

The N-Boc-protected β -amino acids (**IX**) are first transformed into the corresponding acyl azides (**XII**) by reaction of their mixed anhydride (prepared with EtOCOCl/N-methylmorpholine) with NaN₃. The isocyanates (**II**), generated in situ by heating the acyl azide (**XII**) in toluene at 65° are immediately treated with N-hydroxysuccinimide (1 equivalent) in the presence of pyridine (1 equivalent) to give the carbamate (**I**) and (**I bis**). This sequence of reaction from (**IX**) is generally complete in less than one hour (reaction 1).

Reaction 1

25



Reagents: (a) i-BuOCOCl, NMM, -20°C; (b) NaN₃, H₂O; (c) Toluene, 65°C; (d) N-hydroxysuccinimide, pyridine.

The O-succinimidyl carbamates (**I**) and (**Ibis**) crystallize for the most part directly from the solution of toluene at ambient temperature and are obtained simply by filtration with suitable yield. Recrystallization in toluene or another suitable solvent permits obtaining pure specimens for analysis. It is interesting to note that the mild conditions employed are compatible with the use of functionalized side chains (Table 1).

Table 1. Conversion of β -amino acids (**IX**) into O-succinimidyl carbamates (**I**) and (**Ibis**).

R =	Products (I) and (I bis)	Yield (%) ^a	m.p. (°C)	HPLC <i>t</i> _R (min) ^b
H	Ia	55	132-134	6.95
Me	Ib	60	153-155	8.00
<i>i</i> -Pr	Ic	51	125-127	10.80
Bn	Id	55	163-164	12.79
CH ₂ CO ₂ (Bzl)	Ie	58	115-117	13.47
CH(Me)OBzl	If	64	109-110	14.59

^aYield of (**I**) and (**I bis**) after recrystallization.

^bLinear gradient of A (0.1% CF₃COOH in H₂O) and B (MeCN containing 0.08% CF₃COOH), 20-80% B, 20 min. The compound of formula (**I**) and (**I bis**) is that indicated in reaction 1 above.

Starting with 2-nitrobenzoic acid⁸, the corresponding O-succinimidyl carbamate (**Ig**) has been isolated with 71% yield after recrystallization in ethyl acetate. The X-ray structure of the carbamate (**Ig**) (Figure 1) shows that the molecule has an extended configuration with an intra-

molecular hydrogen bond between the adjacent nitro and carbamate groups ($N_2 \cdot O_2$, 2.62 Å). The succinimidyl cycle is turned about 77° relative to the plane of the phenyl cycle.

Carbamates (**I**), (**I bis**) and (**Ig**) are stable crystalline solids which can be stored for months at 4°C without degradation. So as to study the possibilities and limits of the activated monomers of the invention for the preparation of substituted symmetric ureas, different amines and amino acids have been treated with the carbamates (**I**) and (**I bis**). The results are shown in Table 2.

Table 2
Formation of substituted ureas (**VI**) with carbamates (**I**) and (**I bis**)

Entry	Carbamate	Amine	Time (min) ^a	Urea VI	Yield(%) ^b
1	Ia		20		78
2	Ib		20		85
3	Id		20		87
4	Id		30		89

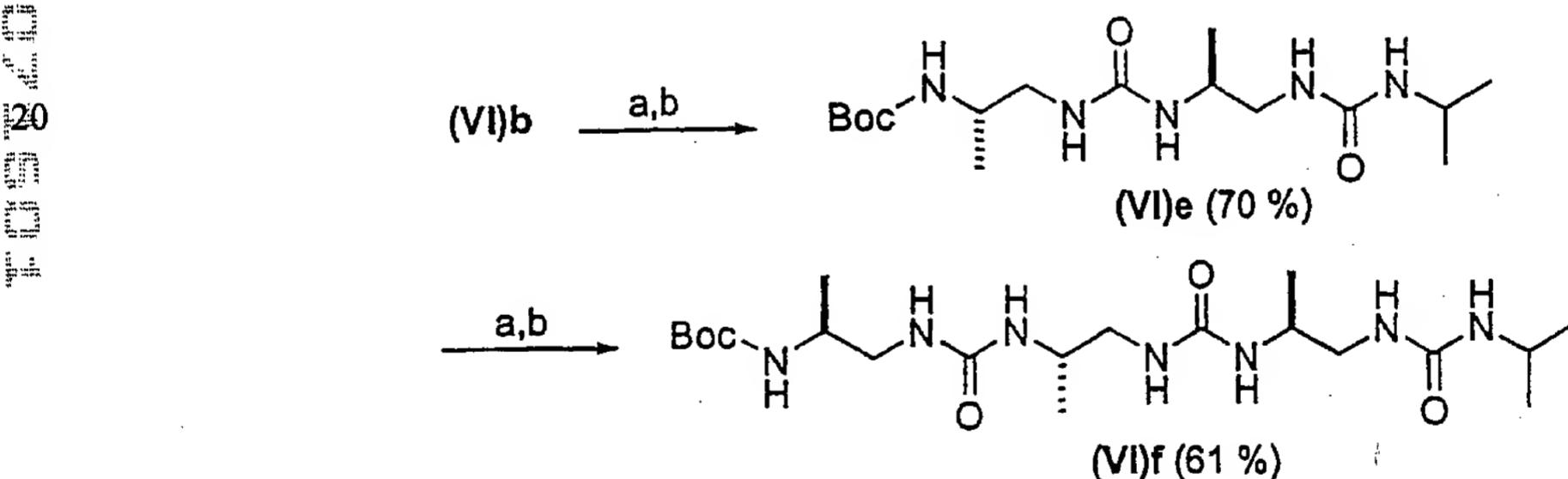
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^a Reaction conditions: carbamate (3 mmol), amine (3-4 mmol), Hunig base (3 mmol), DMF (5 ml), ta.^b yield after purification.

It is found that the carbamates (**I**) and (**I bis**) react with primary amines or amino acids in the presence of Hunig base at ambient temperature to give the corresponding urea derivatives (**VI**) with good yield (table 1, entry 1, 2). The reaction is very rapid and all the initial product is generally consumed in twenty minutes. The N-hydroxysuccinimide is the only secondary product formed during the reaction and is easily eliminated by aqueous washing. Under the same conditions, the aromatic amines such as aniline (entry 3) and a secondary amine (entry 4) also rapidly react with the carbamate (**Id**) to give the respective ureas (**VIc**) and (**VID**).

The repetitive formation of urea by using carbamates (**I**) and (**I bis**) as activated monomers permits obtaining urea oligomers as shown by the synthesis of Boc-A^uCH₂-A^uCH₂-i-Pr (**VIe**) and Boc-A^uCH₂-A^uCH₂-A^uCH₂-i-Pr (**VIIf**). (reaction 2).⁹

Reaction 2



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Reagents (a) TFA; (b) (**Ib**), Hunig base, DMF.

In conclusion, the O-succinimidyl-β-(tert-butoxy-carbonyl-amino)-carbamates (**I**) and (**Ibis**) are easily prepared from β-amino acids and react properly and with good yield with the primary and secondary amines to form urea derivatives. The mild conditions employed for the preparation of carbamates (**I**) and (**Ibis**) are compatible with most of the side chains of the natural amino acids and these stable intermediaries represent synthons attractive

for the synthesis in solid phase of urea peptides and urea oligomers.

Experimental Section

Generalities.

The amino acid derivatives have been bought from Neosystem or Novabiochem. THF is distilled with Na/benzophenone under argon before use. The toluene is distilled over P₂O₅ and preserved on a 4Å molecular sieve. The aniline was passed through an alumina column before use. The Boc-β³-amino acids were prepared according to procedures of the literature¹⁰ by Arndt-Eistert homologation of the commercial protected amino acids. Reactions were conducted under argon pressure. The HPLC analysis was carried out on a Nucleosil C₁₈ column (5 m, 3.9 x 150 mm) by using a linear gradient of A (0.1% CF₃COOH in H₂O) and B (MeCN) at a flow rate of 1.2 ml/min with UV detection at 214 nm.

General procedure for the preparation of O-succinimidyl carbamates (**I**) and (**Ibis**).

The N-protected β-amino acid (10 mmol) is dissolved in THF (30 ml) under argon and cooled to -20°. After addition of i-BuOCOCl (11 mmol) and NMM (11 mmol, 1.1 equivalent), the reaction mixture is agitated at -20° for 20 minutes. The resulting white suspension is reheated to -5°, and is treated with a 5 ml solution of NaN₃ (25 mmol). The mixture is then agitated for 5 minutes, diluted with EtOAc, washed with saturated NaCl, dried on MgSO₄ and concentrated under reduced pressure to give the acyl azide (**XI**) which is used without further purification. The toluene is then added under argon and the resulting solution is heated to 65°C with agitation. Once the emission of gas has stopped (about 10 minutes), the N-hydroxysuccinimide (10 mmol) and the

pyridine (10 mmol) are added. The mixture is agitated for 5 minutes at 65°C and cooled to ambient temperature. In most cases, the desired product crystallizes in the toluene solution and is collected by filtration. Recrystallization in toluene permits obtaining pure O-succinimidyl carbamate. Otherwise, the solvent is evaporated under vacuum and the residue is purified by recrystallization in a suitable solvent.

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O-succinimidyl-2-(tert-Butoxycarbonylamino)-ethyl-carbamate (Ia).

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3-(tert-Butoxycarbonylamino) propanoic acid (3.78 g, 20 mmol) is transformed by following the general procedure. A recrystallization in toluene gives the compound (**Ia**) (3.3g, 50%), constituted by colorless crystals; mp. 132-134°C; HPLC t_R 6.95 minutes (linear gradient, 20-80% B, 20 minutes); $^1\text{H-NMR}$ (200 MHz, DMSO-D₆): 1.38 (s, 9H), 2.76 (s, 4H), 3.00-3.11 (m, 4H), 3.78-3.93 (m, 1H), 6.87 (br t, 1H); 8.27 (t, J = 5.1 Hz, 1H). $^{13}\text{C-NMR}$ (50 MHz, CD₃CN): 171.7, 157.5, 153.1, 79.7, 42.7, 40.6, 28.6, 26.3. MS (MALDI-TOF) (mass spectroscopy: matrix assisted laser desorption ionization - time of flight) m/z 340 [M + K]⁺, 324 [M + Na]⁺. Calculated analysis for C₁₂H₁₉N₃O₆: C, 47.84; H, 6.36; N, 13.95. Found: C, 48.09; H, 6.65; N, 14.00.

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(S)-O-succinimidyl-2-(tert-Butoxycarbonylamino)-propyl-carbamate (Ib).

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Boc- β^3 -HAla-OH (3.25 g, 16 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (**Ib**) (3.05 g, 60% which is a white solid; mp. 153-155°C; $[\alpha]_D^{25} - 14.4$ (c 1.03, MeCN); HPLC t_R 8.00 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CD₃CN): 1.07 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 2.73 (s, 4H), 3.14-3.20 (m, 2H), 3.62-3.72 (m, 1H),

5.25 (br d, 1H), .6.54 (br t, 1H). ^{13}C -NMR (50 MHz, CD₃CN): 171.7, 156.7, 153.3, 79.6, 47.7, 47.4, 28.7, 26.3, 18.4. Calculated analysis for C₁₃H₂₁N₃O₆: C, 49.52 ; H, 6.71 ; N, 13.33. Found: C, 49.45 ; H, 6.57 ; N, 13.18.

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(S)-O-succinimidyl-2-(tert-butoxycarbonylamino)-(II)-methyl-butylcarbamate (Ic).

10 Boc- β^3 -HVal-OH (1.27g, 5.5 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (Ic) (956 mg, 51%) which is a white solid; mp. 125-127°C; $[\alpha]_D^{25} - 41.2$ ($c = 1.15$, THF, CHCl₃); HPLC t_R 10.80 min (linear gradient, 20-80% B, 20 min); ^1H -NMR (200 MHz, CD₃CN): 0.89 (t, $J = 7.0$ Hz, 6H), 1.42 (s, 9H), 1.65-1.78 (m, 1H), 2.73 (s, 4H), 3.11-3.52 (m, 3H), 5.18 (br d, $J = 8.5$ Hz, 1H), 6.46 (br t, 1H). ^{13}C -NMR (50 MHz, CD₃CN): 171.7, 157.7, 153.5, 79.3, 56.7, 44.8, 31.0, 28.7, 26.3, 19.8, 18.3. MS (MALDI-TOF) m/z 383 [M + K]⁺, 367 [M + Na]⁺. Calculated analysis for C₁₅H₂₅N₃O₆: C, 52.47; H, 7.34 ; N, 12.24. Found: C, 52.26 ; H, 7.13 ; N, 11.92.

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(S)-O-succinimidyl-2-(tert-butoxycarbonylamino)-4-phenyl-propylcarbamate (Id).

25 Boc- β^3 -HPhe-OH (8.27g, 29.5 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (Id) (6.6g, 57% yield) which is a white solid; mp. 163-164°C; $[\alpha]_D^{25} - 15$ ($c 1.17$, MeCN); HPLC t_R 12.79 min (linear gradient, 20-80% B, 20 min); ^1H -NMR (200 MHz, CD₃CN): 1.33 (s, 9H), 2.68-2.90 (m, 6H), 3.16-3.37 (m, 2H), 3.78-3.93 (m, 1H), 5.26 (d, $J = 8.0$ Hz, 1H), .6.54 (br t, 1H); 7.16-7.34 (m, 5H). ^{13}C -NMR (50 MHz, CD₃CN): 171.7, 157.3, 153.3, 139.4, 130.3, 129.4, 127.4, 79.6, 53.2, 46.3, 39.0, 28.6, 26.3. MS (MALDI-TOF) m/z 430 [M + K]⁺, 414 [M +

$\text{Na}]^+$. Calculated analysis for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_6$: C, 58.30 ; H, 6.44 ; N, 10.74. Found: C, 58.17 ; H, 6.38 ; N, 10.69.

5 (S)-O-succinimidyl-3-(benzyloxycarbonyl)-2-(tert-butoxycarbonylamino)-propylcarbamate (Ie).

Boc- β^3 -HAsp(Bzl)-OH (2.53g, 7.5 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (**Ie**) (1.94g, 58%) which is a white solid; mp. 115-117°C; $[\alpha]_D^{25} - 16.3$ (c 1.3, THF); HPLC 10 t_R 13.47 min (linear gradient, 20-80% B, 20 min); 1 H-NMR (200 MHz, CD₃CN) : 1.46 (s, 9H), 2.47-2.58 (m, 2H); 2.73 (s, 4H), 3.29 (t, $J = 6.2$ Hz, 2H), 3.96-4.08 (m, 1H), 5.10 (s, 2H), 5.45 (br d, $J = 6.2$ Hz, 1H); 6.54 (br t, 1H); 7.29-7.41 (m, 5H). 13 C-NMR (50 MHz, CD₃CN): 26.3, 28.7, 37.6, 45.8, 48.9, 67.2, 80.0, 118.3, 129.1, 129.6, 137.3, 153.4, 156.5, 171.6, 171.7. MS (MALDI-TOF) m/z 488 [M + K]⁺, 472 [M + Na]⁺. Calculated analysis for C₂₁H₂₇N₃O₈: C, 56.12; H, 6.05; N, 9.35. Found: C, 55.89; H, 6.01; N, 9.32.

(S)-*O*-succinimidyl-3-(benzyloxy)-2-(*tert*-butoxy-carbonylamino)-propylcarbamate (If).

Boc- β^3 -HThr(Bzl)-OH (2.31g, 7.14 mmol) is transformed by following the general procedure. Recrystallization in AcOEt/hexane gives the compound (**If**) (2.0g, 64% yield) which is a white solid; mp. 109-110°C; $[\alpha]_D^{25} + 8.6$ (c 1.07, CH₃CN); HPLC t_R 14.59 min (linear gradient, 20-80% B, 20 min); ¹H-NMR (200 MHz, CD₃CN) : 1.16 (d, $J = 6.1$ Hz, 3H), 1.43 (s, 9H), 2.73 (s, 4H), 3.21-3.44 (m, 2H), 3.61-3.76 (m, 2H), 4.51 (Abq, $J = 11.5$ Hz, 2H), 5.21 (br d, $J = 9.1$ Hz, 1H), 6.49 (br t, 1H), 7.25-7.39 (m, 5H). ¹³C-NMR (50 MHz, CD₃CN) : 16.4, 26.3, 28.6, 44.1, 55.3, 71.5, 75.1, 128.5, 128.8, 129.3. MS (MALDI-TOF) m/z 475 [M + K]⁺, 459 [M + Na]⁺.

Calculated analysis for $C_{21}H_{29}N_3O_7$: C, 57.92 ; H, 6.71 ; N, 9.65. Found: C, 58.02 ; H, 6.67; N, 9.81.

O-succinimidyl-(2-nitrophenyl)carbamate (Ig) (see figure 1).

2-nitrobenzoic acid (1.17g, 7 mmol) is transformed by following the general procedure. Recrystallization in AcOEt gives the compound (**Ig**) (1.39g, 71%) which is present in the form of light yellow crystals; mp. 166-167°C; HPLC t_R 9.45 min (linear gradient, 20-80% B, 20 min); 1H -NMR (200 MHz, $CDCl_3$): 2.89 (s, 4H), 7.26 (dt, 1H), 7.69 (dt, 1H), 8.26 (dd, 1H), 8.40 (dd, 1H), 10.40 (br s). ^{13}C -NMR (50 MHz, $CDCl_3$) : 25.6, 120.8, 124.1, 126.2, 133.1, 136.2, 148.5, 169.2. MS (MALDI-TOF) m/z 318 [M + K]⁺, 302 [M + Na]⁺. Calculated analysis for $C_{12}H_{10}N_2O_6$: C, 47.32 ; H, 3.25 ; N, 15.05. Found: C, 47.45 ; H, 3.26 ; N, 15.07.

Formation of ureas: general procedure.

O-succinimidyl carbamates (**I**) and (**I bis**) (1 mmol) and Hunig base (1 mmol) are added to a solution of the amine (1.3 mmol) in 5 ml DMF. After 10-30 minutes, the reaction mixture is diluted with saturated $NaHCO_3$, and extracted with AcOEt. The organic phase is washed with 1 N $KHSO_4$, saturated NaCl, $NaHCO_3$, saturated NaCl, dried ($MgSO_4$) and evaporated. Chromatography and/or recrystallization give the pure urea (**VI**).

Methyl (2*S*, 3*R*)-2-{[2-(tert-Butoxycarbonylamino)ethyl]-ureido}-3-methyl-pentanoate (Boc-G^uCH₂-Leu-OMe, (VIa**)).**

The carbamate (**Ia**) (602 mg, 2 mmol) is treated with HCl·H-Leu-OMe (436 mg, 2.4 mmol) following the general procedure. Recrystallization in EtOAc/diisopropylether gives (**VIa**) (520 mg, 78%) which is present in the form of colorless needles; mp. 86-89°C; $[\alpha]_D^{25}$ - 10.8 (c 1.02,

MeOH); HPLC t_R 11.39 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CDCl_3): 0.90 (d, $J = 6.4$ Hz, 3H), 0.91 (d, $J = 6.2$ Hz, 3H), 1.41 (s, 9H), 1.45-1.75 (m, 3H), 3.16-3.32 (m, 4H), 3.69 (s, 3H), 4.36-4.47 (m, 1H), 5.34 (br t, $J = 5.2$, 1H), 6.14 (d, $J = 8.2$, 1H), 6.76 (br t, $J = 5.0$, 1H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 21.9, 22.9, 24.8, 28.4, 40.3, 41.3, 41.8, 51.7, 52.1, 79.4, 156.7, 158.5, 175.3. MS (MALDI-TOF) m/z 370 [M + K] $^+$, 354 [M + Na] $^+$, 332 [M + 1] $^+$. Calculated analysis for $\text{C}_{15}\text{H}_{29}\text{N}_3\text{O}_5$: H_2O : C, 52.94 ; H, 8.82 ; N, 12.35. Found: C, 52.92 ; H, 8.68 ; N, 12.27.

(2S)-1-[2-(tert-Butoxycarbonylamino)-propyl]-3-(1-methyl-ethyl)-urea (Boc-A^uCH₂-i-Pr, (VIb)).

The carbamate (**Ib**) (901 mg, 2.86 mmol) is treated with i-PrNH₂ (511 l, 6 mmol) according to the general procedure to give (**VIb**) (701 mg, 95%) which is a white solid; mp. 101°C; $[\alpha]_D^{25} - 7.4$ (c 0.89, MeOH); HPLC t_R 8.71 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CD_3CN): 1.03 (d, $J = 6.6$ Hz, 3H), 1.07 (d, $J = 6.5$ Hz, 6H), 1.40 (s, 9H), 3.02-3.08 (m, 2H), 3.47-3.60 (m, 1H), 3.65-3.81 (m, 1H), 4.92 (br d, 1H); 5.1 (br t, 1H), 5.66 (br, 1H); $^{13}\text{C-NMR}$ (50 MHz, CD_3CN): 158.4, 156.4, 79.4, 47.7, 46.2, 42.2, 28.5, 23.4, 23.3, 18.6. MS (MALDI-TOF) m/z 298 [M + K] $^+$, 282 [M + Na] $^+$. Calculated analysis for $\text{C}_{12}\text{H}_{25}\text{N}_3\text{O}_3$: C, 55.57 ; H, 9.72 ; N, 16.20. Found: C, 55.56 ; H, 9.82; N, 16.16.

(2S)-1-[2-(tert-Butoxycarbonylamino)-3-phenyl-propyl]-3-phenyl-urea (Boc-F^uCH₂-Ph, (VIc)).

The carbamate (**Id**) (500 mg, 1.28 mmol) is treated with PhNH₂ (119 mg, 1.28 mmol) according to the general procedure. A recrystallization in CH_2Cl_2 /hexane gives (**VIc**) (412 mg, 87%) which is a white solid. mp. 154 °C; $[\alpha]_D^{25} + 10.3$ (c 1.03, MeOH); HPLC t_R 15.23 min (linear gradient,

20-80% B, 20 min); $^1\text{H-NMR}$ (400 MHz, CD₃OD): 1.35 (s, 9H), 2.70 (dd, J = 8.0, 13.7 Hz, 1H), 2.80 (dd, J = 7.8, 13.7 Hz, 1H), 3.16 (dd, J = 8.6, 13.6 Hz, 1H), 3.33 (dd, J = 4.6, 17.1 Hz, 1H), 3.81-3.85 (m, 1H), 7.16-7.34 (m, 10H).
 5 $^{13}\text{C-NMR}$ (400 MHz, CD₃OD): 158.8, 158.6, 141.3, 140.1, 130.8, 130.2, 129.8, 127.7, 123.9, 120.7, 80.4, 54.6, 44.8, 40.3, 29.1, 28.8. MS (MALDI-TOF) m/z 408 [M + K]⁺, 392 [M + Na]⁺, 370 [M + 1]⁺. Calculated analysis for C₂₁H₂₇N₃O₃: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.19; H, 7.32; N, 11.47.

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Boc-F^uCH₂-Pro-NH₂, (VI^d) .

The carbamate (I^d) (1.16g, 3 mmol) is treated with HCl·H-Pro-NH₂ (540 mg, 3.6 mmol) according to the general procedure. A chromatography (CHCl₃/MeOH 10:1) gives (VI^d) (1.16g, 88%) which is a white solid; mp. 96-98 °C; $[\alpha]_D^{r.t.}$ -20.4 (c 1.02, MeOH); HPLC t_R 10.02 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CD₃OD): 1.36 (s, 9H), 1.88-2.17 (m, 4H), 2.59-2.83 (m, 2H), 2.96 (dd, J = 9.4, 13.6 Hz, 1H), 3.21-3.50 (m, 3H), 3.89-3.99 (m, 1H), 4.29 (dd, J = 3.2, 8.1 Hz, 1H), 7.11-7.29 (m, 5H). $^{13}\text{C-NMR}$ (200 MHz, CDCl₃): 24.7, 28.4, 28.8, 39.0, 45.7, 46.3, 51.6, 60.1, 79.6, 126.6, 128.6, 129.2, 137.4, 156.6, 157.8, 175.4. MS (MALDI-TOF) m/z 429 [M + K]⁺, 413 [M + Na]⁺, 391 [M + 1]⁺. Calculated analysis for C₂₀H₃₀N₄O₄: C, 61.52; H, 7.74. Found: C, 61.78 H, 7.77.

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Boc-A^uCH₂-A^uCH₂-i-Pr, (VI^e) .

The product (VI^b) (650 mg, 2.5 mmol) is dissolved in CF₃COOH (0.25M) at 0°. After agitation at ambient temperature for 30 minutes and concentration under reduced pressure, the trifluoroacetate salt is dried under vacuum under KOH and used without further purification.

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The carbamate (**Ib**) is treated with a solution of trifluoroacetate salt according to the general procedure. Recrystallization in EtOH/hexane gives (**VIe**) (630 mg, 70%) which is a white solid. mp. 184-185°C, $[\alpha]_D^{25}$ + 9.3 (c 0.88, MeOH); HPLC t_R 8.52 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CD₃OD): 1.05-1.12 (m, 12H), 1.42 (s, 9H), 2.92-3.24 (m, 4H), 3.56-3.84 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CD₃OD): 160.9, 160.7, 158.2, 80.0, 48.2, 47.8, 46.8, 46.4, 42.9, 28.5, 23.6, 23.5, 19.1, 18.6. Calculated analysis for C₁₆H₃₃N₅O₄: C, 53.46; H, 9.25; N, 19.48. Found: C, 53.62; H, 9.29; N, 19.43.

Boc-A^uCH₂-A^uCH₂-A^uCH₂-i-Pr, (VIf).

The product (**VIe**) (440 mg, 1.22 mmol) is dissolved in CF₃COOH (0.25M) at 0°. After agitation at ambient temperature and concentration under reduced pressure the trifluoroacetate salt, which precipitates by addition of Et₂O, is collected by filtration, dried under vacuum under KOH and is used without further purification.

To a solution of this salt in DMF are added successively (**Ib**) and Hunig base (637 l, 3.66 mmol). The reaction mixture is agitated for 20 minutes and saturated NaHCO₃ is added. The precipitate which forms is filtered, washed with saturated NaHCO₃, water, and Et₂O and is dried under vacuum on P₂O₅ to give (**VIf**) (350 mg, 62%) which is a white solid. mp. 210-211°C, $[\alpha]_D^{25}$ 63.6 (c 1.00, MeOH); HPLC t_R 8.53 min (linear gradient, 20-80% B, 20 min); $^1\text{H-NMR}$ (200 MHz, CD₃OD): 1.03-1.12 (m, 15H), 1.44 (s, 9H), 2.55-2.85 (m, 3H), 3.21-3.39 (m, 3H), 3.61-3.95 (m, 4H); $^{13}\text{C-NMR}$ (100 MHz, CD₃OD): 161.2, 161.1, 160.9, 158.7, 80.3, 48.2, 47.6, 47.5, 47.2, 47.1, 46.8, 43.0, 29.0, 23.8, 23.7, 19.5, 19.0, 18.7. MS (MALDI-TOF) m/z 499 [M + K]⁺, 483 [M + Na]⁺,

461 [M + 1]⁺. Calculated analysis for C₂₀H₄₁N₇O₅: C, 52.27; H, 8.99; N, 21.33. Found: C, 52.23; H, 9.00; N, 20.93.

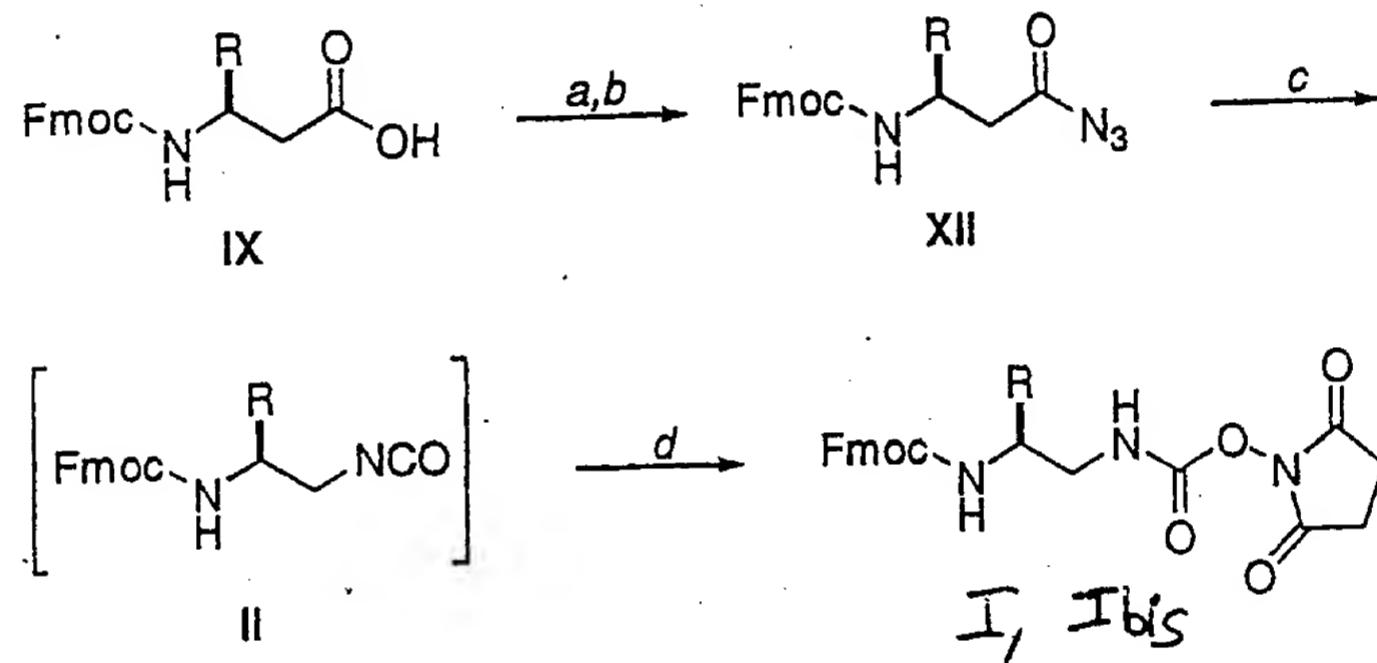
Example II:

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Preparation of O-succinimidyl-2-[(9H-fluoren-9-yl-ethoxy) carbonylamino]-ethylcarbamate derivatives from β -amino acids and application to the synthesis in solid phase of oligoureas and of pseudopeptide urea:

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1) Preparation of O-succinimidyl carbamates (**I**) and (**Ibis**).



Reaction 1. Reagents and conditions: a) EtOCOCl, NMM, THF, -15°C, 15 min; (b) NaN₃, H₂O, 5 min (c) Toluene, 65°C; (d) N-hydroxysuccinimide, pyridine, 65°C, 5 min.

In accordance with reaction 1, the N-Fmoc-protected β -amino acids (**IX**) comprising side chains of natural amino acids Ala, Val, Leu, Phe, Tyr, et Lys are converted into the corresponding acyl azides (**XII**) by reaction of their mixed anhydride (formed with EtOCOCl/N-methyl morpholine (NMM)) with an aqueous solution of NaN₃ (2.5 equiv). The intermediate isocyanates (**II**) obtained by Curtius rearrangement on (**XII**) (toluene, 65°C, 5 to 15 min) are immediately treated with N-hydroxysuccinimide (1 equivalent) in the presence or not of pyridine (1 equivalent) to give the carbamates (**I**) and (**Ibis**) as

crystalline products (see the yield in Table 1). As in the case of the Boc derivatives (see example 1), this reaction sequence is generally complete in 1 hour. As has been shown for the Boc-protected derivatives, the carbamates (**I**) and (**Ibis**) precipitate or recrystallize directly from the toluene solution and are simply collected by filtration. In the case of these Fmoc protected derivatives, the yields obtained (51-86%) are better than with the corresponding Boc derivatives.

Similarly, these carbamates (**I**) and (**Ibis**) can be stored at ambient temperature or at 4°C without noticeable degradation.

Table 1 shows the conversion of β -amino acids (**IX**) into the corresponding O-succinimidyl carbamates (**I**) and (**I bis**).

^a Yield of (**I**) and (**I bis**) after recrystallization from toluene. ^b linear gradient of A (0.1% TFA in H₂O) and B (MeCN containing 0.08% TFA), 30-100% B, 20 min.

R =	Carbamates (I) and (Ibis)	Yield (%) ^a	mp (°C)	[α] ²⁵ _D (c, DMF)	HPLC <i>t</i> _R (min) ^b
Me	Ih	86	161-163	-3.6 (c = 1.08)	10.44
iPr	Ii	69	109-111	+5.9 (c = 1.18)	11.84
iBu	Ij	51	134-137	-10.8 (c = 1.01)	12.63
Bn	Ik	66	175-177	-26.1 (c = 1.13)	12.48
Bn(OtBu)	Il	78	138-140	-22.9 (c = 1.12)	13.87
(CH ₂) ₄ NH(Boc)	Im	79	122-124	-4.7 (c = 1.16)	12.67

Procedure for obtaining O-succinimidyl carbamates (**I**) and (**I bis**).

The N-protected β -amino acid (10 mmol) is dissolved in THF (30 ml) under Ar and cooled to -20°. After addition of i-BuOCOCl (11 mmol) and NMM (11 mmol, 1.1. equivalent), the reaction mixture is agitated at -20° for 20 minutes. The resulting white solution is reheated to -5°, and is treated with a solution (5 ml) of NaN₃ (25 mmol). The mixture is

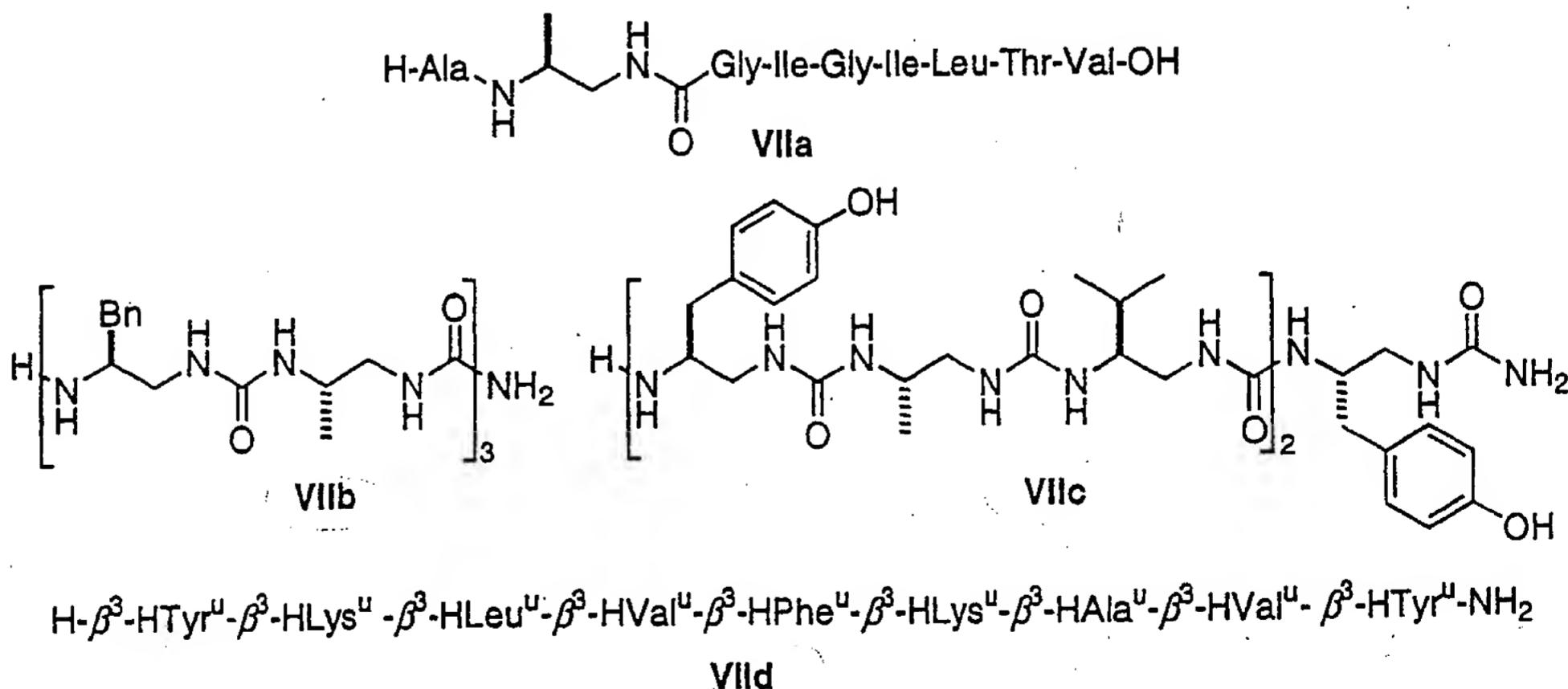
then agitated for 5 minutes, diluted with EtOAc, washed with saturated NaCl, dried on MgSO₄ and concentrated under reduced pressure to give the acyl azide which is used without further purification. Toluene is then added under argon and the resulting solution is heated to 65°C with agitation. Once the emission of gas has ceased (about 10 minutes), the N-hydroxysuccinimide (10 mmol) and the pyridine (10 mmol) are added. The mixture is agitated for 5 minutes at 65°C and cooled to ambient temperature. In most cases, the desired product crystallizes in the toluene solution and is collected by filtration. Recrystallization in toluene permits obtaining pure O-succinimidyl carbamate. Otherwise, the solvent is evaporated under vacuum and the residue is purified by recrystallization in the appropriate solution.

2) Application to synthesis on a solid support

With monomers (Ih)-(Im), the aim was the preparation of ureidopeptide (VIIa) and oligoureas (VIIb)-(VIIc) containing six to nine urea linkages.

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(The abbreviations used for the derivative (VIIId) are defined in reference 9).

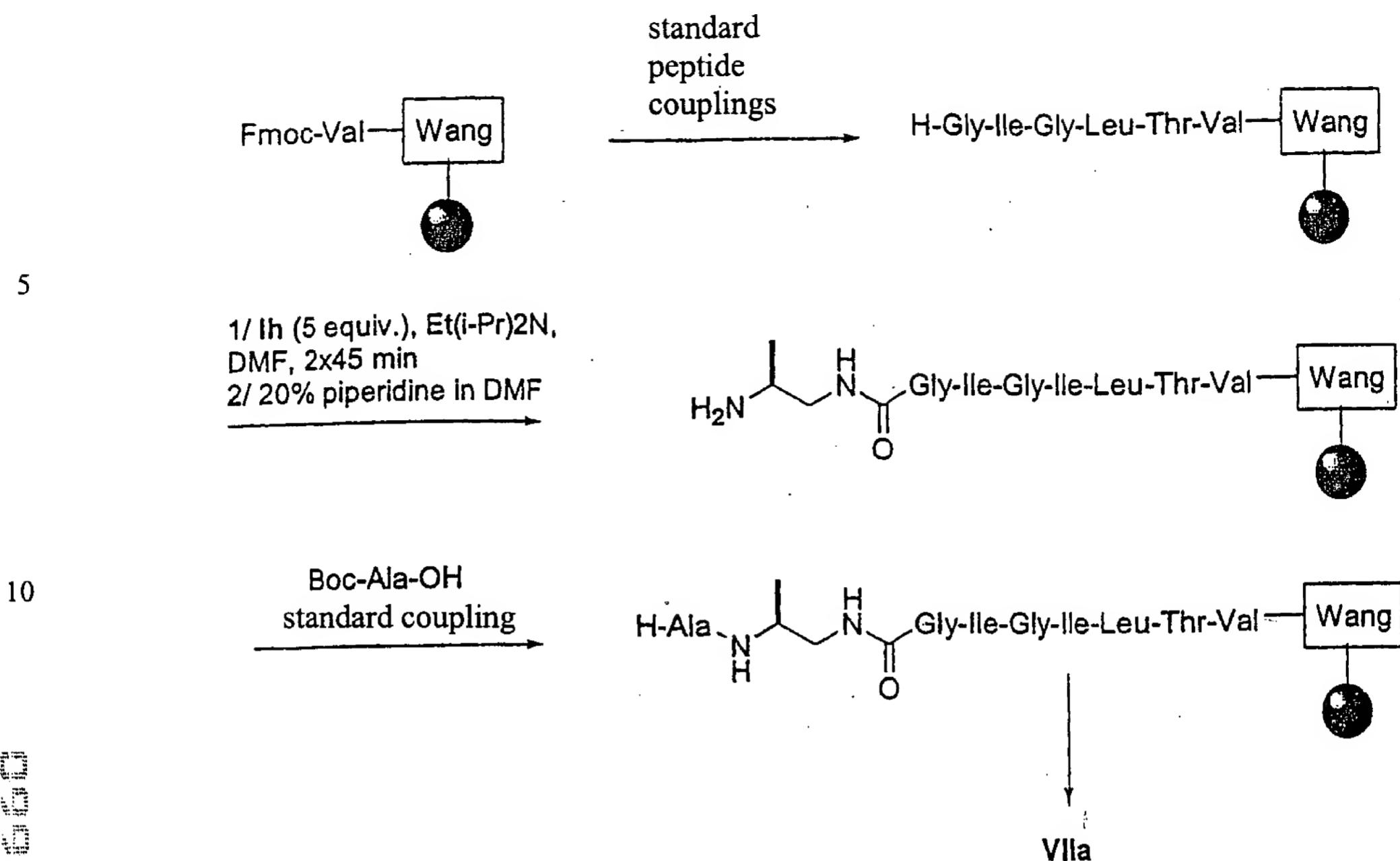
Incorporation of a urea structure in a peptide.

The peptide sequence selected by way of example is that of the tumoral antigen MART(27-35) of the sequence:

5 H-Ala-Ala-Gly-Ile-Gly-Ile-Leu-Thr-Val-OH.

The use of the carbamate (**Ih**) has permitted the introduction of a urea structure between Ala²⁸ and Gly²⁹.

10 The synthesis in solid phase of the peptide up to Gly²⁹ is carried out by Fmoc chemistry (Fluorenyl methoxycarbonyl) on a scale of 100 moles by starting with a Wang resin (p-benzyloxybenzyl alcohol) substituted with valine according to conventional methods of synthesis of peptides in solid phase (References: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed: G.B. Fields, Academic Press, NY, USA). After deprotection of the Fmoc group of Gly²⁹ with 20% piperidine in DMF, the carbamate (**Ih**) (5 equivalents) dissolved in DMF followed by diisopropylethylamine (5 equivalents) are added to the resin, and the reaction is left to proceed for 45 minutes. This operation can if desired be repeated once. After washing and rinsing of the resin, the Fmoc group is deprotected as above, and Fmoc-Ala-OH is coupled to the resin by using methods described in the literature (references: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed: G.B. Fields, Academic Press, NY, USA).

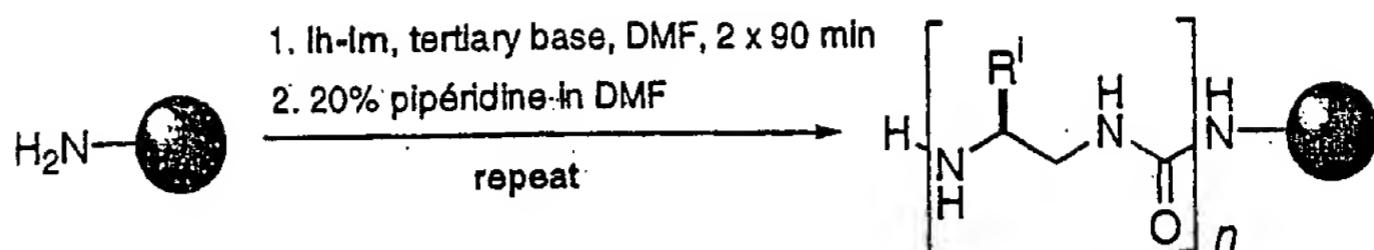


After cleaving the resin by conventional protocols used in peptide synthesis in solid phase (references: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed.: G.B. Fields, Academic Press, NY, USA), the desired crude product (**VIIa**) is obtained after lyophilization with a purity of 73% (by HPLC) (see table 2 below). After purification by HPLC and lyophilization, the product is obtained with a purity of 99.2%. The pure product is characterized by mass spectrometry (MALDI-MS) and by HPLC.

Synthesis of urea oligomers from O-succinimidyl carbamates of formula (I) and (I bis).

The general synthesis reaction of oligoureas (**VIIb**) - (**VIId**) is shown in reaction 2. The products (**VIIb**) - (**VIId**) have been synthesized in solid phase from a commercial Rink amide resin (4-(2',4'-dimethoxyphenyl-Fmoc-amino-methyl)phenoxyacetamido-4-methylbenzhydrylamine resin) (0.60 mequiv/g) on a scale of 100 μmole.

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Reaction 2. General procedure for synthesis in solid phase of oligoureas by using *O*-succinimidyl carbamates (**I**) and (**I bis**).

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The carbamates (**Ih**) to (**Im**) (5 equiv.) in 2ml of DMF are added to a suspension of the resin in DMF (2ml) followed by diisopropylethylamine (5 equiv.). The reaction is left to run 90 minutes and repeated, after filtration of the resin. The Fmoc group is then cleaved by treated with 20% piperidine in DMF. The washing and filtration techniques of the resin as well as the deprotection of the Fmoc group are those currently used in peptide synthesis in solid phase. The whole operation (coupling and deprotection of the Fmoc) is repeated several times with carbamates (**Ih**) and (**Im**) alternating, to give, after cleavage of the resin (standard cleavage used in peptide synthesis in solid phase with the Fmoc strategy) the crude products (**VIIb**) to (**VIId**) with good yield.

The purity of the crude products is given in Table 2 below. The HPLC purification on a C18 column, followed by lyophilization, gives pure products (**VIIb**) - (**VIId**) with an overall yield comprised between 20 and 50% (Entries 1-4 of Table 2).

Entry	Product	Base	HPLC crude purity (%)	Global yield (%) ^a	HPLC <i>t</i> _R (min) ^b	MALDI-TOF MS
1	VIIa	DIEA	73	50	12.57 ^c	842.9 [M+H] ⁺
2	VIIb	DIEA	63	42	10.86 ^d	846.8 [M+H] ⁺
3	VIIc	DIEA	51	38	14.58 ^c	1051.5 [M+H] ⁺
4	VIID	DIEA	35	20	15.14 ^c	1393.0 [M+H] ⁺
5	VIIc	NMM	66	57	14.70 ^c	1073.2 [M+Na] ⁺
6	VIIc	-	61	55	14.59 ^c	1072.8 [M+Na] ⁺

Table 2. Characterization of ureidopeptide (**VIIa**) and oligoureas (**VIIb**) - (**VIID**). ^aafter purification and lyophilization. ^blinear gradient of A (0.1% TFA in H₂O) and B (MeCN containing 0.08% TFA). ^c5-65% B, 20 min. ^d20-80% B, 20 min.

The quantity of impurities present in the raw product of synthesis increases with the size of the oligomer. Analysis by MALDI-TOF-MS shows that the principal impurities isolated by HPLC on a C18 column arise either from deletions (products of lower mass that can result from incomplete couplings or else incomplete deprotection of the Fmoc group in the latter stages of synthesis), or more surprisingly by double insertion of monomers. A study of the stability of the carbamates (**Ih**) - (**Im**) in the solutions of DMF containing 5% diisopropylethylamine (DIEA) shows substantial degradation as well as partial cleavage of the Fmoc group. Based on these results, more gentle conditions for the reaction have been evaluated. On the one hand, the use of a weaker tertiary base such as N-methyl morpholine (NMM) gives better results (entry 5 of table 2). On the other hand, it has been shown that the use of a tertiary base was not necessary because good results are obtained in the absence of a base by using identical reaction times (see entry 6 of table 2).

In conclusion, there has been described an effective method for the preparation of optically active O-succinimidyl - (9H-fluoren-9-ylmethoxycarbonylamino)-ethyl carbamate derivatives (**Ih**)-(**Im**) and their use as activated monomers in the synthesis in solid phase of oligoureas.

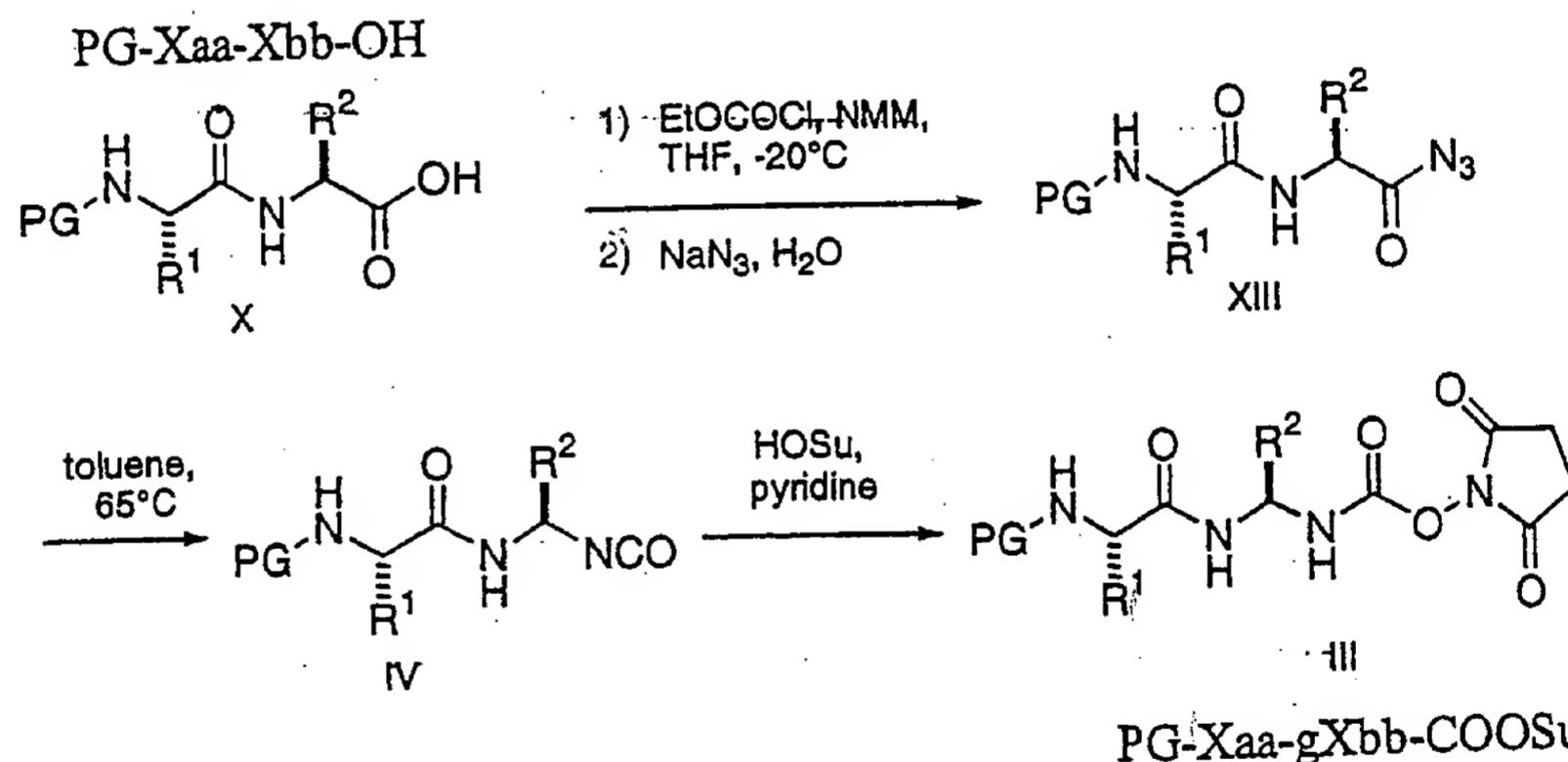
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Example III

Preparation of O-succinimidyl carbamate derivatives (**III**) and (**III bis**) from N-protected dipeptides and application to the synthesis of ureido peptide and hybrid peptide/oligoureas.

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1) Preparation of O-succinimidyle carbamates (**III**) and (**III bis**)



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Reaction 1: Synthesis of O-succinimidyl derivatives (**III**) and (**III bis**) from N-protected dipeptides.

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In accordance with reaction 1, the N-Boc or N-Fmoc protected dipeptides (**X**) comprising side chains of natural amino acids Ala, Val, Leu, Phe, Tyr, and Lys, are converted into corresponding acyl azides (**XIII**) by reaction of their mixed anhydride (formed with EtOCOCl/N-methyl morpholine (NMM) with an aqueous solution of NaN₃ (2.5 equivalent).

The intermediate isocyanates (**IV**) obtained by Curtius rearrangement on (**XIII**) (toluene, 65°C, 5 to 15 minutes) are immediately treated with N-hydroxysuccinimide (1 equivalent) in the presence or not of pyridine (1 equivalent) to give carbamates (**III**) and (**III bis**) as crystalline products (see the yields in Table 1). As in examples I and II, this reaction sequence is generally complete in 1 hour. As has been shown for the Boc-protected β -amino acid derivatives, the carbamates (**III**) and (**III bis**) precipitate or recrystallize directly from the toluene solution and are simply collected by filtration. In the case of dipeptide derivatives, the yields obtained (52-93%) are good to excellent.

Similarly, these carbamates (**III**) and (**III bis**) can be stored at ambient temperature or at 4°C without notable degradation.

Original Dipeptides	Carbamates (III) and (III bis)	Yield (%) ^a	HPLC <i>t</i> _R (min) ^b	MALDI-TOF MS
Boc-Gly-Ile-OH	IIIa	87	9.13 ^c	-
Boc-Pro-Val-OH	IIIb	72	11.79 ^e	-
Boc-Phe-Leu-OH	IIIc	82	14.01 ^c	513.46 [M+Na] ⁺
Boc-Ile-Val-OH	IIId	62	13.46 ^e	-
Boc-Lys-Val-OH	IIIe	69	14.98 ^c	-
Boc-Pro-Leu-OH	IIIf	76	12.73 ^e	-
Boc-Phe-Pro-OH	IIIg	80		
Fmoc-Ile-Leu-OH	IIIh	93	12.85 ^d	601.29 [M+Na] ⁺
Fmoc-Phe-Ala-OH	IIIi	86	11.45 ^d	593.32 [M+Na] ⁺
Fmoc-Ile-Gly-OH	IIIj	52	10.94 ^d	545.05 [M+Na] ⁺

Table 1. Conversion of dipeptides (**X**) into the corresponding O-succinimidyl carbamates (**III**) and (**III bis**).

^a yields of (**III**) and (**III bis**) after recrystallization from toluene. ^b linear gradient of A (0.1% TFA in H₂O) and B (MeCN containing 0.08% TFA), ^c 20-80% B, 20 min, ^d 30-100% B, 20 min, ^e 0-100% B, 20 min.

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Procedure for obtaining O-succinimidyl carbamates (III**) and (**III bis**).**

The N-protected dipeptide (10 mmol) is dissolved in THF (30 ml) under Ar and cooled to -20°. After addition of i-BuOCOCl (11 mmol) and NMM (11 mmol, 1.1 equivalent), the reaction mixture is agitated at -20° for 20 minutes. The resulting white solution is reheated to -5°, and is treated with a solution (5 ml) of NaN₃ (25 mmol). The mixture is then agitated for 5 minutes, diluted with EtOAc, washed with saturated NaCl, dried on MgSO₄, and concentrated under reduced pressure to give the acyl azide which is used without further purification. The toluene is then added under argon and the resulting solution is heated 65°C with agitation. Once the generation of gas has stopped (about 10 minutes), the N-hydroxysuccinimide (10 mmol) and the pyridine (10 mmol) are added. The mixture is agitated for 5 minutes at 65°C and cooled to ambient temperature. In most cases, the desired product crystallizes from the toluene solution and is collected by filtration. Recrystallization in toluene permits obtaining pure O-succinimidyl carbamate. Otherwise, the solvent is evaporated under vacuum and the residue is purified by recrystallization in the suitable solvent.

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Experimental section

General remarks:

HPLC analyses have been carried out on a C₁₈ column (5 µm, 3.9 x 150 mm by using a gradient of A (0.1% TFA in H₂O)

and B (0.08% TFA in MeCN) at a flow rate of 1.2 ml/min with UV detection at 214 nm.

Boc-Gly-gIle-COOSu (IIIA) :

Yield 87% white solid; HPLC t_r 9.13 (linear gradient, 5 20-80% B, 20 min) - ^1H RMN ($[\text{D}_6]\text{DMSO}$, 200 MHz) : δ = 0.79-0.95 (m, 6H, $\text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}_3$), 0.98-1.14 (m, 2H, $\text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}_3$), 1.38 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.60-1.78 (m, 1H, $\text{CH}_3-\text{CH}-\text{CH}_2-\text{CH}_3$), 2.77 (s, 4H, CH_2-CH_2), 3.50-3.68 (m, 2H, NHCH_2CO), 10 5.00-5.20 (m, 1H, $\text{NH}-\text{CH}-\text{NH}$), 6.90-7.00 (m, 1H, $\text{NHCO}_2\text{C}(\text{CH}_3)_3$), 7.99 (d, J = 8.6 Hz, 1H, NHCO_2Su), 8.54 (d, J = 8.0 Hz, 1H, NHCOCH). - ^{13}C RMN ($[\text{D}_6]\text{DMSO}$, 50 MHz) : δ = 170.7 (CO), 168.7 (CO), 155.7 (CO), 150.8 (CO), 78.0 (C), 61.4 (CH), 43.0 (CH₂), 38.1 (CH), 28.0 (CH₃), 25.2 (CH₂), 24.3 (CH₂), 14.2 (CH₃), 10.7 (CH₃).

Boc-Phe-gLeu-COOSu (IIIC) :

Yield 82% white solid; HPLC t_r 14.01 (linear gradient, 20 20-80% B, 20 min) - ^1H RMN ($[\text{D}_6]\text{DMSO}$, 200 MHz) : δ = 0.87 (d, J = 5.4 Hz, 3H, CH₃), 0.88 (d, J = 5.4 Hz, 3H, CH₃), 1.29 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.50-1.73 (m, 3H, $\text{CH}-\text{CH}_2-\text{CH}-\text{(CH}_3)_2$), 2.64-2.98 (m, 2H, $\text{CH}_2-\text{C}_6\text{H}_5$), 2.76 (s, 4H, CH_2-CH_2), 4.04-4.21 (m, 1H, CHCO), 5.32 (m, 1H, NHCHNH), 6.85 (d, J = 8.6 Hz, 1H, $\text{NHCO}_2\text{C}(\text{CH}_3)_3$), 7.10-7.30 (m, 5H, C₆H₅), 8.25 (d, J = 8.3 Hz, 1H, NHCO_2Su), 8.65 (d, J = 7.5, 1H, NHCOCH). - ^{13}C RMN ($[\text{D}_6]\text{DMSO}$, 50 MHz) : δ = 171.0 (C), 170.7 (C), 155.2 (C), 150.2 (C), 138.1 (C), 129.2 (CH), 127.9 (CH), 126.1 (CH), 77.9 (C), 56.4 (CH), 55.5 (CH), 42.9 (CH₂), 37.1 (CH₂), 28.0 (CH₃), 25.2 (CH₂), 23.8 (CH), 22.2 (CH₃), 21.9 (CH₃).

Boc-Lys(2ClZ)-gVal-COOsu (IIIe)

Yield 69% white solid; HPLC t_r 14.98 (linear gradient, 20-80% B, 20 min) - ^1H RMN ($[\text{D}_6]\text{DMSO}$) : δ = 0.84 (d, J = 6.2 Hz, 3H, Me), 0.87 (d, J = 5.4 Hz, 3H, Me), 1.15-1.57 (m, 6H, $\text{CHCH}_2\text{CH}_2\text{CH}_2$), 1.34 (s, 9H, *t*-Bu), 1.72-1.98 (m, 1H, Me_2CH), 2.72 (s, 4H, CH_2CO), 2.85-3.08 (m, 2H, CH_2NH), 3.78-3.92 (m, 1H, NHCHCO), 4.87-4.99 (m, 1H, NHCHNH), 5.06 (s, 2H, OCH_2), 6.82 (d, J = 8.2 Hz, 1H, $\text{NHCO}_2(t\text{-Bu})$), 7.24-7.50 (m, 5H, H arom.), 7.93 (d, J = 8.7 Hz, 1H, NHCO_2Su), 8.54 (d, J = 7.9 Hz, 1H, CHCONHCH). - ^{13}C RMN ($[\text{D}_6]\text{DMSO}$, 50 MHz) : δ = 171.6, 170.6, 150.9, 150.8, 134.5, 132.0 (C), 129.6, 129.2, 127.2 (CH), 77.9 (C), 62.8 (CH), 62.4 (CH_2), 54.1 (CH), 40.0 (CH_2), 31.8 (CH), 31.2, 29.0 (CH_2), 28.1 (CH_3), 25.2, 22.7 (CH_2), 18.2, 18.0 (CH_3).

Fmoc-Phe-gAla-COOsu (IIIf)

Yield 86% white solid ; HPLC t_r 11.45 (linear gradient, 30-100% B, 20 min) - ^1H RMN ($[\text{D}_6]\text{DMSO}$, 200 MHz) : δ = 1.31 (d, J = 6.5 Hz, Me), 2.65-2.77 (m, 5H, CH_2CO , NCHCH_2), 2.75 (br dd, 1H, NCHCH_2), 4.04-4.25 (m, 4H, CHCH_2O , CHCO), 5.31 (m, 1H, NHCHNH), 7.13-7.41 (m, 9 arom. H), 7.47-7.63 (m, 3H, arom. H, NHCOO_2Fm), 7.84 (d, J = 7.3 Hz, 2 arom. H), 8.53 (d, J = 7.8 Hz, 1H, NHCO_2Su), 8.72 (d, J = 7.0 Hz, 1H, CHCONHCH). - ^{13}C RMN ($[\text{D}_6]\text{DMSO}$, 50 MHz) : δ = 170.7, 155.7, 150.3, 143.7, 140.6, 138.2 (C), 129.1, 127.9, 127.5, 127.0, 126.1, 125.2, 120.0 (CH), 65.5 (CH_2), 55.8, 54.5, 46.5 (CH), 37.3, 25.2 (CH_2), 20.5 (CH_3).

Fmoc-Ile-gGly-COOsu (IIIf)

Yield 52% white solid ; HPLC t_r 10.94 (linear gradient, 30-100% B, 20 min) - ^1H RMN ($[\text{D}_6]\text{DMSO}$, 200 MHz) : δ = 0.80

(t, $J = 7.0$ Hz, 3H, Me), 0.83 (d, $J = 6.6$ Hz, 3H, Me), 1.01-1.23 (m, 1H, CH_2Me), 1.34-1.50 (m, 1H, CH_2Me), 1.59-1.82 (m, 1H, CHMe), 2.76 (s, 4H, CH_2CO), 3.91 (t, $J = 8.0$ Hz, 1H, CHCH_2O), 4.22-4.30 (m, 3H, CHCH_2O , NHCH), 4.35-4.55 (m, 2H, NHCH₂), 7.28-7.46 (m, 4H, arom. H, NHCO_2Fm), 7.75 (d, $J = 6.9$ Hz, 2 arom. H), 7.89 (d, $J = 7.0$ Hz, 2 arom. H), 8.69 (br. t, $J = 5.6$ Hz, 1H, NHCO_2Su), 9.00 (br. t, $J = 8.0$ Hz, 1H, CHCONHCH_2). - ^{13}C RMN ([D₆] DMSO, 50 MHz) : $\delta = 171.7, 170.6, 155.8, 151.9, 143.7, 140.6$ (C), 127.5, 126.9, 125.3, 120.0 (CH), 65.6 (CH₂), 58.8, 46.6 (CH), 45.6 (CH₂), 36.3 (CH), 25.2, 24.3 (CH₂), 15.2, 10.7 (CH₃).

Boc-Pro-gLeu-COOsu (IIIf)

Yield 76% white solid; HPLC t_r 10.59 (linear gradient, 20-80% B, 20 min) - ^1H RMN ([D₆] DMSO, 200 MHz) : $\delta = 0.83$ (d, $J = 6.0$ Hz, 6H, $\text{CH}-(\text{CH}_3)_2$), 1.28, 1.34 (s, 9H, C(CH₃)₃), 1.45-1.52 (m, 3H, $\text{CH}-\text{CH}_2-\text{CH}-(\text{CH}_3)_2$), 1.59-2.05 (m, 4H, $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}$), 2.72 (s, 4H, CH_2-CH_2), 3.14-3.36 (m, 2H, N-CH₂-CH₂), 4.02-4.05 (m, 1H, NCHCO), 5.17-5.27 (m, 1H, NHCHNH), 8.19 (d, $J = 8.0$ Hz, 1H, NHCO_2Su), 8.57 (d, $J = 7.3$, 1H, NHCOCH). - ^{13}C RMN ([D₆] DMSO, 50 MHz) : $\delta = 171.73$ (C), 171.69 (C), 153.18 (C), 150.45 (C), 78.26 (C), 59.14 (CH), 56.35 (CH), 46.40 (CH₂), 42.78 (CH₂), 30.88 (CH₂), 27.91 (CH₃), 25.20 (CH₂), 23.82 (CH), 22.85 (CH₂), 22.27 (CH₃), 21.87 (CH₃).

Boc-Pro-gVal-COOsu (IIIB)

Yield 72% white solid; HPLC t_r 8.98 (linear gradient, 20-80% B, 20 min) - ^1H RMN ([D₆] DMSO, 200 MHz) : $\delta = 0.87$ (d, $J = 6.4$ Hz, 6H, $\text{CH}-(\text{CH}_3)_2$), 1.31, 1.37 (s, 9H, C(CH₃)₃), 1.74-2.07 (m, 5H, $\text{CH}-\text{CH}-(\text{CH}_3)_2$, $\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2$), 2.74 (s, 4H, CH_2-CH_2), 3.17-3.32 (m, 2H, N-CH₂-CH₂), 4.10-4.13 (m, 1H, NCHCO), 4.88-5.04 (m, 1H, NHCHNH), 8.08 (d, $J = 8.5$ Hz,

1H, NHCO₂Su), 8.49 (d, *J* = 7.8 Hz, 1H, NHCOCH). - ¹³C RMN ([D₆] DMSO, 50 MHz) : δ = 171.84 (C), 170.66 (C), 153.28 (C), 150.80 (C), 78.31 (C), 62.91 (CH), 59.19 (CH), 46.42 (CH₂), 31.61 (CH), 30.97 (CH₂), 27.98 (CH₃), 25.16 (CH₂), 5
22.81 (CH₂), 18.23 (CH₃).

Boc-Ile-gVal-COOsu (IIIId)

Yield 62% white solid; HPLC *t*_r 11.67 (linear gradient, 20-80% B, 20 min) - ¹H RMN ([D₆] DMSO, 200 MHz) : δ = 0.64-10 0.91 (m, 12H, CH-(CH₃)₂, CH₃-CH-CH₂-CH₃), 0.97-1.05 (m, 1H, CH₃-CH-CH₂-CH₃) 1.27-1.37 (s, 10H, C(CH₃)₃, CH₃-CH-CH₂-CH₃), 1.56-1.63 (m, 1H, CH₃-CH-CH₂-CH₃), 1.80-1.94 (m, 1H, CH-CH-(CH₃)₂), 2.70 (s, 4H, CH₂-CH₂), 3.71-3.79 (m, 1H, NH-CH-CO), 4.87-4.99 (m, 1H, NHCHNH), 6.66 (d, *J* = 8.9Hz, 1H, NHBoc), 7.98 (d, *J* = 8.7 Hz, 1H, NHCO₂Su), 8.53 (d, *J* = 8.1 Hz, 1H, NHCOCH). - ¹³C RMN ([D₆] DMSO, 50 MHz) : δ = 170.97 (C), 170.60 (C), 155.27 (C), 150.82 (C), 77.89 (C), 62.73 (CH), 58.64 (CH), 36.07 (CH), 31.67 (CH), 28.07 (CH₃), 25.18 (CH₂), 24.31 (CH₂), 18.34 (CH₃), 18.13 (CH₃), 15.24 (CH₃), 20 10.73 (CH₃).

Fmoc-Ile-gLeu-COOsu (IIIf)

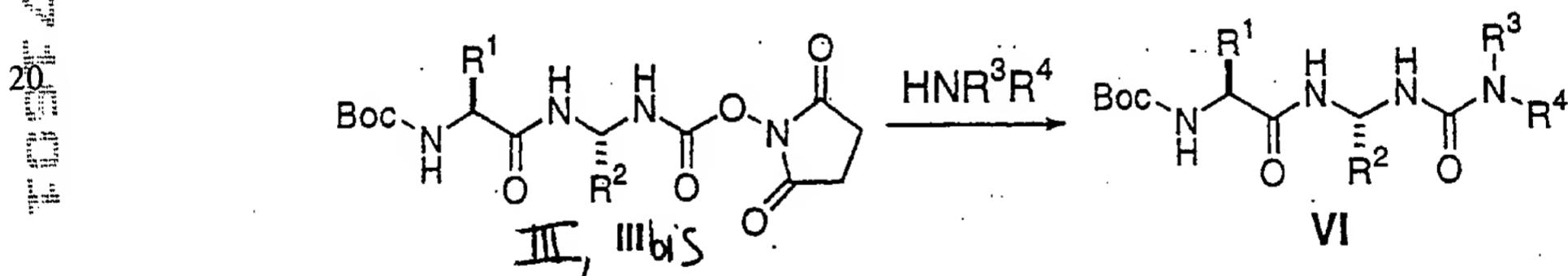
Yield % white solid; HPLC *t*_r 12.85 (linear gradient, 30-100% B, 20 min) - ¹H RMN ([D₆] DMSO, 200 MHz) : δ = (m, 12H, CH-(CH₃)₂, CH₃-CH-CH₂-CH₃), (m, 1H, CH₃-CH-CH₂-CH₃) (s, 10H, C(CH₃)₃, CH₃-CH-CH₂-CH₃), 1.56-1.63 (m, 1H, CH₃-CH-CH₂-CH₃), 1.80-1.94 (m, 1H, CH-CH-(CH₃)₂), 2.70 (s, 4H, CH₂-CH₂), 3.71-3.79 (m, 1H, NH-CH-CO), 4.87-4.99 (m, 1H, NHCHNH), 6.66 (d, *J* = 8.9Hz, 1H, NHBoc), 7.98 (d, *J* = 8.7 Hz, 1H, NHCO₂Su), 8.53 (d, *J* = 8.1 Hz, 1H, NHCOCH). - ¹³C RMN ([D₆] DMSO, 50 MHz) : δ = 170.97 (C), 170.60 (C), 155.27 (C), 150.82 (C), 77.89 (C), 62.73 (CH), 58.64 (CH), 36.07

(CH), 31.67 (CH), 28.07 (CH₃), 25.18 (CH₂), 24.31 (CH₂), 18.34 (CH₃), 18.13 (CH₃), 15.24 (CH₃), 10.73 (CH₃).

5 **2) Reactivity of carbamates (III) and (III bis) with amines and amino acids to give urea dipeptides or ureidopeptides.**

10 It is seen that the carbamates (III) and (IIIBis) react with primary amines or amino acids in the presence of absence of a tertiary base (DIEA, NMM, Et₃N) at ambient temperature to give corresponding urea derivatives (VI) (Reaction 2) with good yields (table 2). The reaction is rapid and all the starting product is generally consumed in several hours. The N-hydroxysuccinimide is the only secondary product formed during the reaction and is easily eliminated by aqueous washing.

Reaction 2: Synthesis of ureas (VI) from carbamates (III) and (IIIBis).



25 **Table 2:** Reactivity of carbamates (III) and (III bis) to give ureas (VI).

^a yield of (VI). ^b linear gradient of A (0.1% TFA in H₂O) and B (MeCN containing 0.08% TFA), ^c 20-80% B, 20 min, ^d 30-100% B, 20 min, ^e 0-100% B, 20 min.

Carbamate (III) and (III bis)	amine	Urea (VI)	Yield (%) ^a	HPLC <i>t</i> _R (min) ^b	MALDI-MS
III f	HN(Me) ₂	Boc-Pro-gLeu-CON(Me) ₂		c	
III f	HNMe	Boc-Pro-gLeu-CONHMe		e	
III f	H-Phe-OMe	Boc-Pro-gLeu-CO-Phe-OMe	92	15.1 ^e	
III e	H ₂ N(<i>i</i> -Pr)	Boc-Lys(2-Cl-Z)-gVal-CONH(<i>i</i> -Pr)	70	15.60 ^e	593.06 [M + Na] ⁺
III e	HN(Bn) ₂	Boc-Lys(2-Cl-Z)-gVal-CON(Bn) ₂	74	18.25 ^e	731.68 [M + Na] ⁺
III d	H-Pro-Me	Boc-Ile-gVal-CO-Pro-OMe	93	13.9 ^e	

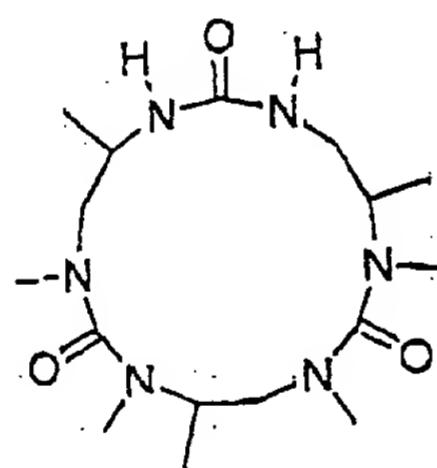
The repetitive formation of urea by using carbamates (III) and (III bis) as activated monomers permits obtaining hybrid oligoureapptides.

EXAMPLE IV

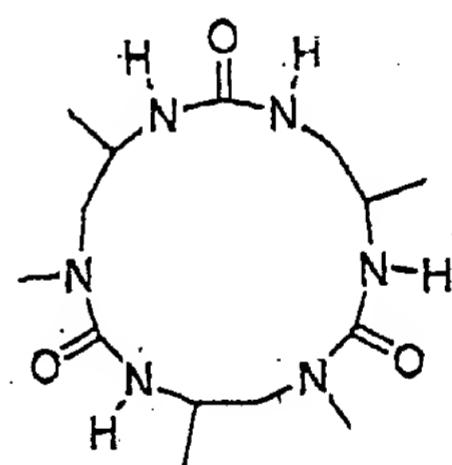
Examples of cyclic compounds corresponding to the formula (VIII bis) :

THERMOCHEMISTRIES

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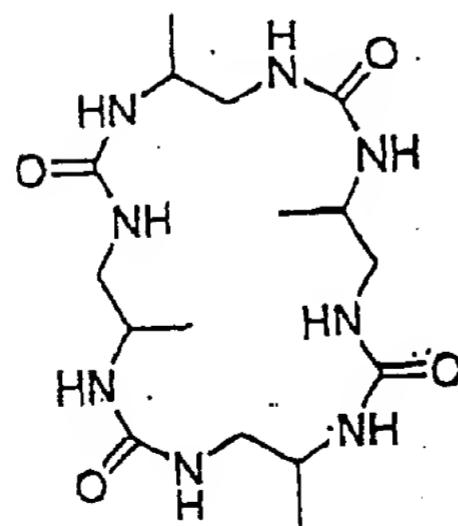


(VIII bis/1)

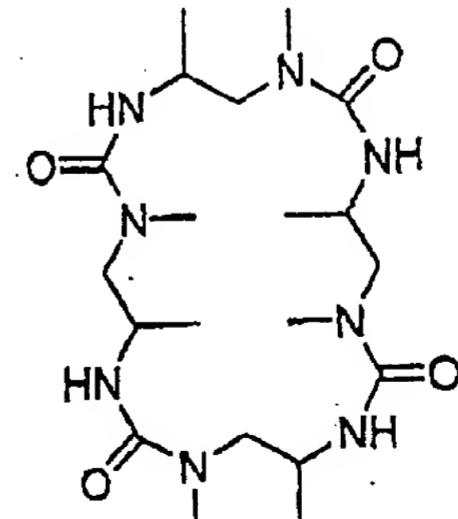


(VIII bis/2)

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(VIII bis/3)

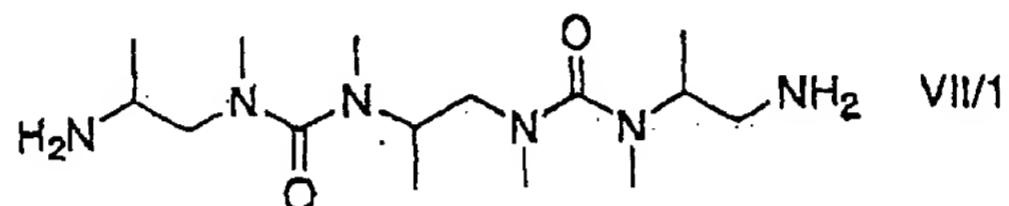


(VIII bis/4)

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The compound (**VIII bis/1**) can for example be synthesized by intramolecular cyclization of the linear precursor hereinafter corresponding to the formula (**VII/1**) (1 mmol) by treatment with carbonyldiimidazole (1 mmol) in acetonitrile (200 ml) and in the presence of an excess of DIEA (2.5 mmol) for 12 hours.

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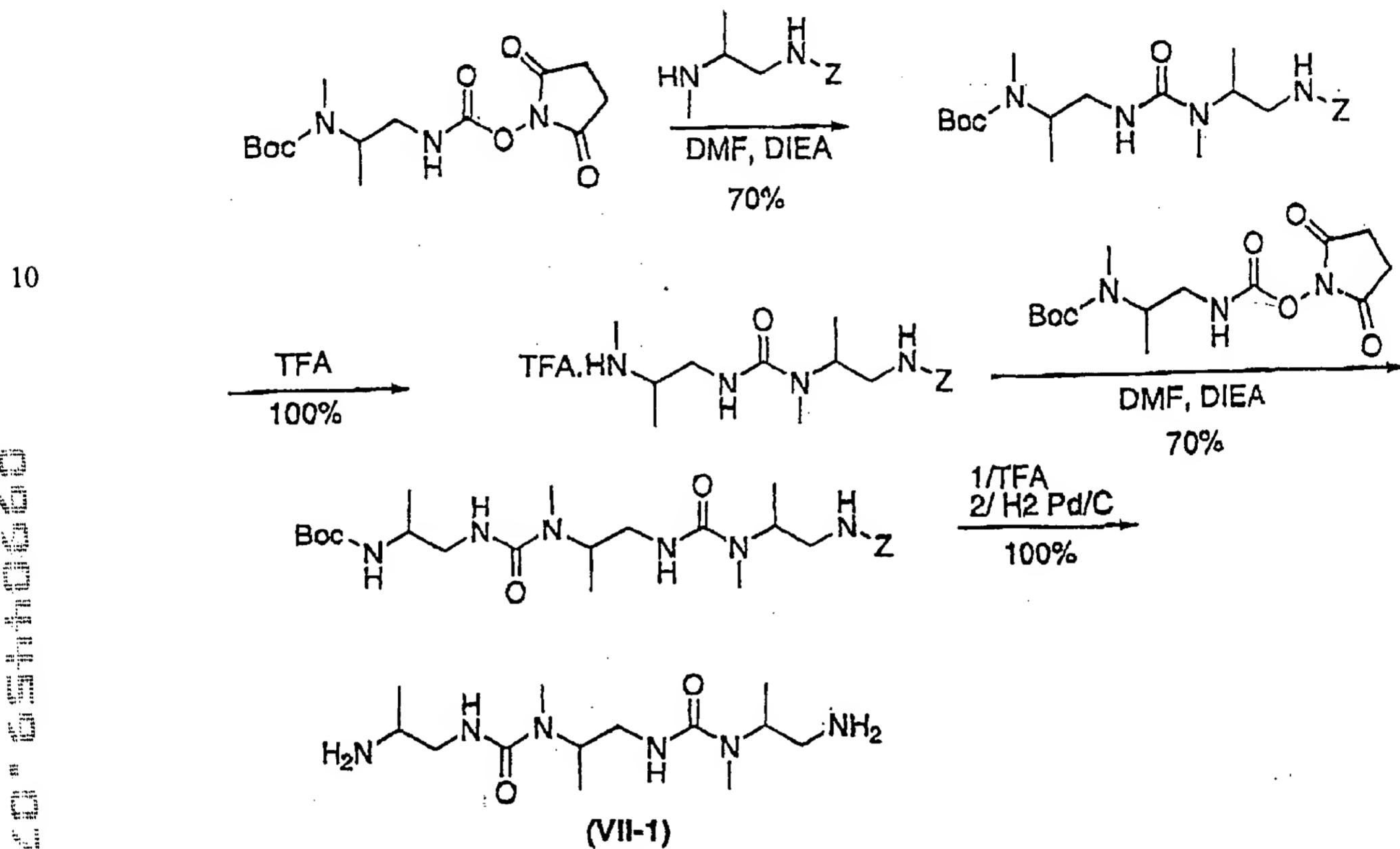
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After this time, the solvent is evaporated and the residue is purified by liquid chromatography in inverse phase (C18 column) using a linear water/acetonitrile gradient.

The linear precursor (**VII/1**) can be prepared according to reaction 1 below. The reaction of a first activated carbamate derived from an N-methylated beta amino acid on a monoprotected diamine, leads to the obtention of a trisubstituted monourea. The deprotection of the Boc group and the repeated reaction of the O-succinimidyle carbamate previously used, leads to the obtention of a di-urea. The successive deprotection of the protective groups Boc and Z gives the derivative (**VII/1**).

Reaction 1: Synthesis of the linear precursor (**VII-1**) used in the synthesis of the compound (**VIII bis/1**) (DMF = dimethylformamide, DIEA = diisopropylethylamine, TFA = trifluoroacetic acid)

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PREPARED IN DR. J. H. WILSON'S LABORATORY

REFERENCES

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- 5 (1) (a) Lam P. Y.; Jadhav P. K.; Eyermann C. J. ; Hodge C. N.; Ru Y., Bacheler L.T.; Meek J. L.; Otto M. J.; Rayner M. M.; Wong Y. N.; Chang, C. -H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994** 263, 380. (b) Castro J. L.; Ball R. G.; Broughton H. B.; Russell M. G., Rathbone D, Watt A. P., Baker R, Chapman K. L., Fletcher A. E., Patel S, Smith A. J., Marshall G. R., Ryecroft W, Matassa V.G. *J. Med. Chem.* **1996**, 39(4):842 (c) von Geldern T.W., Kester J. A., Bal R, Wu-Wong J.R., Chiou W, Dixon D.B., Opgenorth T.J. *J. Med. Chem.* **1996** 39, 968.
- 10 (2) (a) Nowick, J. S.; Smith, E. M.; Noronha, G. W. *J. Org. Chem.* **1995** 60, 7386. (b) Nowick, J. S.; Mahrus, S.; Smith, E. M.; Ziller, J. W. *J. Am. Chem. Soc.* **1996** 118, 1066. (c) Nowick, J. S.; Holmes, D. L.; Mackin, G.; Noronha, G; Shaka, A. J.; Smith, E. M. *J. Am. Chem. Soc.* **1996** 118, 2764. (d) Holmes, D. H.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997** 119, 7665.
- 25 (3) (a) Burgess, K.; Linthicum, Shin, H. *Angew. Chem. Int. Ed. Engl.* **1995** 34, 907. (b) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997** 119, 1556. (c) Kim, J. -M.; Bi, Y.; Paikoff, S. J.; Schultz, P. G. *Tetrahedron Lett.* **1996** 37, 5305. (d) Kim, J. -M.; Wilson, T. E.; Norman, T. C.; Schultz, P. G. *Tetrahedron Lett.* **1996**, 37, 5309. (e) Kruijtzer J. A. W.; Lefeber, D. J.; Liskamp, R. M. J. *Tetrahedron Lett.* **1997** 38, 5335. (f) Wilson, M. E.; Nowick, J. S. *Tetrahedron Lett.* **1998** 39, 6613.

(4) Use of the phosgene and its derivatives, see: (a), Majer, P.; Randad, R. S.; *J. Org. Chem.* **1994** 59, 1937. (b) Scialdone, M. A.; Shuey, S. W.; Soper, P.; Hamuro, Y.; Burns, D. M. *J. Org. Chem.* **1998** 63, 4802-4807. Carbonates, see: (c) Takeda, K.; Akagi, Y.; Saiki, A.; tsukahara, T.; Ogura, H. *Tetrahedron Lett.* **1983** 24, 4569. Izdebski, J.; Pawlak, D. *Synthesis* **1989**, 423. N, N' carbodiimidazole, see: (d) Zhang, X.; Rodrigues, J.; Evans, L.; Hinckle, B.; Ballantyne, L.; Pena. *J. Org. Chem.* **1997** 62, 6420. 1,1'-carbonylbisbenzotriazole, see: (e) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997** 62, 4155.

(5) (a) Nowick, J. S.; Powell, N. A.; Nguyen, T. M.; Noronha, G. *J. Org. Chem.* **1992** 57, 7364. (b) Reference 3b.

(6) (a) Martinez, J.; Oiry, J.; Imbach, J. -L., winternitz, F. *J. Med. Chem.* **1982** 25, 178. (b) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1994** 35, 4055. (c) Thavonekham, B. *Synthesis* **1997**, 1189.

(8) It is interesting to note that in the synthesis of oligoanthranilamides, the Hamilton group uses 2-nitrobenzoic acid in place of N-benzoylanthranillic acid. In this case, the nitro group as the masking group of the amine it is necessary to avoid the formation of azlactone: Hamuro, Y.; Geib, S.J.; Hamilton, A.D. *J. Am. Chem. Soc.* **1996** 118, 7529.

(9) We have used the code with a letter proposed by Burgess for the urea oligomers^{3b}. As an alternative, we propose the following abbreviation which permits the use of the code with a letter for the amino acids: Boc(- β^3 -HAla^u)₂-i-Pr (**VIe**) and Boc(- β^3 -HAla^u)₃-i-Pr (**VIf**). According to the

nomenclature of Spatola¹¹ for the pseudopeptides, we can also write: Boc(- β^3 -HAla-[NHCONH])₂-i-Pr (**VIe**) et Boc(- β^3 -HAla-[NHCONH])₃-i-Pr (**VIIf**).

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(10) (a) Podlech, J.; Seebach, D. *Liebigs Ann.* 1995, 1217. (b) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* 1996 79, 913.

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(11) Spatola, A. F. In *Chemistry and Biochemistry of Amino acids, peptides and Proteins*; Weinstein, B. Ed.; Marcel Dekker Inc.: New York, 1983; Vol. 7, pp267-357.

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